

# ENHANCING NIH RESEARCH ON AUTOIMMUNE DISEASE

Committee for the Assessment of NIH Research  
on Autoimmune Diseases

Board on Population Health and Public Health Practice

Health and Medicine Division

A Consensus Study Report of  
*The National Academies of*  
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## Reviewers

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **BETTY A. DIAMOND**, The Feinstein Institute for Medical Research, and **ALAN I. LESHNER**, American Association for the Advancement of Science (AAAS). They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

## Preface

As a practicing gastroenterologist, I treated patients who had Crohn's disease and ulcerative colitis. Both are inflammatory bowel diseases (IBD) and among the most common autoimmune diseases. Over the last two decades, we have made progress in diagnosing IBD, but we have not yet identified biomarkers that enable us to screen for it. We have made revolutionary advances in targeting pharmaceutical therapies to manage IBD, but these options are still limited, many patients have refractory disease, and the therapies themselves may have significant side effects. There is currently no cure for IBD, so for much of their lives, patients may be at risk for developing additional autoimmune diseases as well as complications such as cancer, infections, and maternal/fetal complications. During the course of this study, I was also reminded that we do not have reliable U.S. incidence and prevalence data for IBD.

A goal of autoimmune disease research is to empower physicians to more accurately diagnose, treat, minimize, and ideally, cure disease. There is a critical research gap in personalized medicine, for example, the ability to measure a combination of individual genetics, serologies, phenotypes, and biological mechanisms that predict response to a specific therapy. Side effects and eventual failures, over time, of current medications dictate a need for continuing research into disease pathogenesis and candidate therapeutics.

Congressional legislation has often assisted in focusing National Institutes of Health (NIH) efforts to meet urgent demands related to the health

and welfare of U.S. citizens. In 2019 Congress called for NIH to contract with the National Academies of Sciences, Engineering, and Medicine to identify and review NIH's research efforts in the broad area of autoimmune diseases with a particular emphasis on the risk factors, diagnostic tools, barriers to diagnosis, treatments, and prospects for cure. Given the complexity of autoimmune diseases and the fact that they encompass many conditions, the committee's expertise included clinicians and researchers in numerous specialties that focus on autoimmune diseases as well as epidemiologists, health disparities researchers, and persons familiar with NIH's research administration processes.

NIH has conducted research that has contributed significantly to the advances in care of autoimmune disease, and it is important to continue to translate research knowledge into more precise diagnostic criteria and clinical interventions to achieve the best outcomes and benefit the lives of our patients. Progress in medical research requires visionary strategic thinking, the ability to meet constant challenges in disease prevention and therapeutics, new findings in genetics, coordination, and interdisciplinary guidance.

The recommendations of the committee in Chapter 7 are preceded by a thoughtful analysis of Institute and Center (IC) autoimmune disease research activity along with the committee findings and conclusions. The number and complexity of these diseases requires a concerted strategic effort that leverages the many research activities that occur across ICs. The committee identifies opportunities and options for enhancing autoimmune disease research at NIH. The committee's recommendations provide a basis for developing a strategy with metrics that yield data that can be reviewed periodically. It is our hope that a subsequent review would show advancement in autoimmune disease research and improvements in outcomes.

On behalf of the committee, I would like express our thanks for the responsiveness of NIH's ICs and Offices in aiding the committee to gather information. A special thanks to Lisa Begg (Office of the Director/Office of Research on Women's Health), Susan Cooper (National Institute of Allergy and Infectious Diseases [NIAID]), and Ellen Goldmuntz (NIAID) for their guidance and support.

I would also like to thank the committee members for their tremendous commitment and hard work, all the more meaningful in view of increased responsibilities both in their practices and their lives as a result of the pandemic, and the need to meet and work together virtually.

On behalf of the committee, I would like to express our thanks and appreciation to the National Academies leadership and staff: Rose Marie

Martinez, Senior Director of the Board on Population Health and Public Health Practice, and acting Study Director; Kristin White, Associate Program Officer; Dara Rosenberg, Research Associate; and Grace Reading, Senior Program Assistant. I would also like to thank former staff members Awo Osei-Anto, Senior Program Officer and Leila Meymand, Senior Program Assistant for their contributions to the study process.

Bernard M. Rosof, M.D., Chair, Committee on the Assessment of NIH Research on Autoimmune Diseases



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## Acronyms and Abbreviations

25OHD	25-hydroxyvitamin D
AARDA	American Autoimmune Related Diseases Association <sup>1</sup>
ACE	Autoimmunity Centers of Excellence
ACF	Administration for Children and Families
ACL	Administration for Community Living
ACP	American College of Physicians
ACR	American College of Rheumatology
AD-ADRD	Alzheimer's Diseases and Alzheimer's Disease Related Dementias
ADCC	NIH Autoimmune Diseases Coordinating Committee
AHRQ	Agency for Healthcare Research and Quality
AI	artificial intelligence
AIDS	acquired immune deficiency syndrome
AIM	autoimmune and immune-mediated diseases
AIT	autoimmune thyroiditis
ALP	alkaline phosphatase
ALPS	autoimmune lymphoproliferative syndrome
AMA	antimitochondrial antibodies
AMP®	Accelerating Medicines Partnership®
ANCA	antineutrophil cytoplasmic antibodies

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<sup>1</sup> In 2021, AARDA changed its name to The Autoimmune Association.

Anti SSA/Ro	anti Sjögren's syndrome related antigen A autoantibodies
Anti SSB/La	anti Sjögren's syndrome related antigen B autoantibodies
APECED	autoimmune polyendocrinopathy candidiasis ectodermal dystrophy
aPL	antiphospholipid antibodies
APS	antiphospholipid antibody syndrome
APS-ACTION	Antiphospholipid Antibody Syndrome Alliance for Clinical Trials and International Networking
AS	ankylosing spondylitis
ASBT	apical sodium-dependent bile acid transport
ASPE	HHS Assistant Secretary for Planning and Evaluation
ATD	autoimmune thyroid disease
ATSDR	Agency for Toxic Substances and Disease Registry
B&F	Buildings and Facilities
BA	Budget Authority
BARDA	Biomedical Advanced Research and Development Authority
BPA	bisphenol A
BRAIN	Brain Research through Advancing Innovative Neurotechnologies Initiative
BRIDA	BACH2-Related Immunodeficiency and Autoimmunity
CAPS	catastrophic antiphospholipid syndrome
CAR	chimeric antigen receptor
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CC	NIH Clinical Center
CD	Crohn's disease
CD40	cluster of differentiation 40
CDC	Centers for Disease Control and Prevention
CeD	celiac disease
CHOP	Children's Hospital of Philadelphia
CIT	Clinical Islet Transplantation Consortium
CMS	Centers for Medicare & Medicaid Services
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRD	Committee RePORTER Datasets
CRS	Congressional Research Service
cSLE	childhood-onset systemic lupus erythematosus

CSR	Center for Scientific Review
CVD	cardiovascular disease
DAIDS	Division of AIDS Research
DAISY	Diabetes Autoimmunity Study in the Young
DAIT	Division of Allergy, Immunology, and Transplantation
DCCT/EDIC	Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications
DED	dry eye disease
DGP	deamidated gliadin peptide
DIPP	Type 1 Diabetes Prediction and Prevention Study
DNA	deoxyribonucleic acid
DOC	dental, oral, craniofacial
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
EAE	experimental autoimmune encephalomyelitis
EAP	Expanded Access Program
EBV	Epstein-Barr virus
ELISA	enzyme-linked immunoassay
EmA	immunofluorescent anti-edmysium
EPA	Environmental Protection Agency
ERA	Electronic Research Administration
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FIC	Fogarty International Center
FOA	funding opportunity announcement
FXR	Farnesoid X Receptor
FY	fiscal year
GGT	gamma-glutamyl transferase
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRSA	Health Resources and Services Administration
HSS	Hospital of Special Surgery
IBD	inflammatory bowel disease
IC	NIH Institute or Center

ICD	International Classification of Diseases
iEdison	Interagency Edison Database
IFNs	interferons
Ig	immunoglobulin
IHS	Indian Health Services
IL	interleukin
IMSGC	International Multiple Sclerosis Genetics Consortium
IOM	Institute of Medicine
IRP	National Institutes of Health Intramural Research Program
ISN	International Society of Nephrology
ITN	Immune Tolerance Network
JAK	Janus kinase inhibitor
JIA	juvenile idiopathic arthritis
JIF	journal impact factor
LDA	latent dirichlet allocation
LFA	Lupus Foundation for America
LFT	liver function tests
LHHS	Labor, Health, and Human Services
LFWG	Lupus Federal Working Group
MG	myasthenia gravis
MGNet	Myasthenia Gravis Rare Disease Network
MOG-Antibody	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
NAM	National Academies of Medicine
NASEM	National Academies of Sciences, Engineering, and Medicine
NCAPG	National Coalition of Autoimmune Patient Groups
NCATS	National Center for Advancing Translational Sciences
NCCIH	National Center for Complementary and Integrative Health
NCI	National Cancer Institute
NEI	National Eye Institute
NHANES	National Health and Nutrition Examination Survey
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging

NIAID	National Institute of Allergy and Infectious Diseases
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIADAR	National Institute of Autoimmune Disease and Autoimmunity Research
NIAMS	National Institute of Allergy and Infectious Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	<i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communications Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
NLP	natural language processing
NMSS	National Multiple Sclerosis Society
NOD	non-obese diabetic
NORD	National Organization of Rare Diseases
norUDCA	norursodeoxycholic acid
NOSI	notice of special interest
NPP	National Priorities Partnership
NPSLE	neuropsychiatric systemic lupus erythematosus
NQF	National Quality Forum
NSAIDs	nonsteroidal anti-inflammatory drugs
OAD/AR	Office of Autoimmune Disease / Autoimmunity Research
OAR	Office of AIDS Research
OBSSR	Office of Behavioral and Social Sciences Research
OCA	obeticholic acid
OD	Office of the Director
OPA	Office of Portfolio Analysis

OS	Office of the Secretary
ORWH	Office of Research on Women's Health
PA	program announcement
pANCA	perinuclear anti-neutrophil cytoplasmic antibody
PBC	primary biliary cholangitis (historically: primary biliary cirrhosis)
PPAR	peroxisome proliferated activated receptor
PROMIS®	Patient-Reported Outcomes Measurement Information System
PROTECT	Study Predicting Response to Standardized Pediatric Colitis Therapy
PSC	primary sclerosing cholangitis
RA	rheumatoid arthritis
RCDC	NIH Research, Condition, and Disease Categorization
RCR	relative citation ratio
RCT	randomized controlled trial
RePORT	Research Portfolio Online Reporting Tools
RePORTER	NIH Research Portfolio Expenditures and Results system
RF	rheumatoid factor
RFA	request for applications
RFI	request for information
RFP	request for proposals
RHYTHM	Rheumatoid Arthritis Study of the Myocardium
RNA	ribonucleic acid
RPS	Renal Pathology Society
SAMHSA	Substance Abuse and Mental Health Services Administration
SARS-COV-2	severe acute respiratory syndrome Coronavirus 2
SEER	Surveillance, Epidemiology, and End Results
SGMRO	Sexual and Gender Minority Research Office
sJIA	systemic juvenile idiopathic arthritis
SLE	systemic lupus erythematosus
SpA	spondyloarthropathy
SPIRES	Scientific Publication Information Retrieval and Evaluation System
SRG	Scientific Review Group
SRO	Scientific Review Officer
SSc	systemic sclerosis

ST	suppression of tumorigenicity
STTR	small business technology transfer
T1D	type 1 diabetes
TEDDY	The Environmental Determinants of Diabetes in the Young
Th	t helper
TLR	toll-like receptor
TNF	tumor necrosis factor
TPN	total parenteral nutrition
TRAPS	tumor necrosis factor receptor-associated periodic syndrome
tTG	tissue transglutaminase
tTGA	tissue transglutaminase autoantibodies
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
USPTO	U.S. Patent and Trade Office
VA	Department of Veterans Affairs
VEXAS	vacuoles, E1 enzyme, X-linked, autoinflammatory and somatic syndrome
WHO	World Health Organization



# Summary<sup>1</sup>

Autoimmune diseases occur when the body's immune system, which normally defends the body against disease and infection, malfunctions and mistakenly attacks healthy cells, tissues, and organs. Common autoimmune diseases include celiac disease, rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease (IBD), and type 1 diabetes. Autoimmune diseases are chronic and lifelong and can cause significant physical and psychosocial impairment, impeding activities of daily living, productivity, and quality of life. They can occur at any age, and many, but not all, predominantly affect women, with female-to-male ratios reaching 6:1 or higher for some diseases. Autoimmune diseases as a group rank among the 10 leading causes of death for females. Individuals with an autoimmune disease commonly develop more than one autoimmune disease, and they can be at increased risk of developing cancer and cardiovascular disease as well as a wide variety of other illnesses and complications. There are no known cures for autoimmune diseases.

There is no consensus on what illnesses are autoimmune diseases; counts range from more than 80 to 150 diseases depending on the source. Definitional boundaries of autoimmunity and autoimmune disease are evolving, and there are differing approaches to characterizing autoimmune diseases—one based on clinical criteria and another based on underlying biological mechanisms. The diseases are heterogeneous in

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<sup>1</sup> References are not included in the report summary. Please view the body of the report for a full list of works cited.

presentation, and using stringent clinical criteria can impede the optimal design of clinical trials and studies as well as the diagnosis and care of patients.

Strong epidemiologic data of the U.S. incidence and prevalence of autoimmune diseases in the past 10–20 years are limited, and a lack of population-based data is of particular concern. The last study that considered autoimmune diseases as a whole in the United States was published in 2009 and estimated the prevalence of autoimmune diseases to be 7.6 to 9.4 percent—or 25 to 31 million people today.<sup>2</sup> However, this estimate was based on only 29 autoimmune diseases, and it does not account for increases in prevalence in the past decade. The impact of autoimmune diseases is significant, and trend data are showing an increasing incidence and/or prevalence of most autoimmune diseases the committee examined, including in children, in whom an increased prevalence of inflammatory bowel disease (IBD) and type 1 diabetes were observed in the past decade. The earlier an autoimmune disease manifests, the longer an individual must live with accruing damage, increased risks of complications and other conditions, and adverse effects on quality of life. No single pattern of racial and ethnic disparities is seen in incidence or prevalence among autoimmune diseases; for some conditions, the highest rates occur among Black, American Indian, and Alaska Native populations, while for others, the highest rates occur in White populations. Disparities in the severity and prognosis of autoimmune diseases have been observed as well as disparities in the provision of care. There is little data on the direct and indirect costs in the United States of specific autoimmune diseases or of autoimmune diseases overall. However, one study found the annual direct costs of multiple sclerosis to be second only to congestive heart failure, and another estimated the average total lifetime cost for patients with Crohn’s disease, an IBD, to be \$622,056. Congressional interest in autoimmune diseases, driven largely by constituents, advocacy groups, and other stakeholders, is longstanding, and congressional requests and mandates have contributed to the trajectory of National Institutes of Health (NIH) autoimmune disease research.

## CHARGE TO THE COMMITTEE

In response to a congressional request, NIH asked the National Academies of Sciences, Engineering, and Medicine to form an expert committee

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<sup>2</sup> Based on 2020 U.S. Census of 331.4 million people. Available at <https://www.census.gov/library/stories/2021/08/united-states-adult-population-grew-faster-than-nations-total-population-from-2010-to-2020.html> (accessed December 22, 2021).

to assess NIH research activities on autoimmune diseases with a particular emphasis on the risk factors, diagnostic tools, barriers to diagnoses, treatments, and prospects for cures. The committee's task also included considering the occurrence of multiple autoimmune diseases in individuals and the interplay of the diseases with comorbidities, as well as identifying barriers to NIH-sponsored research, research gaps, and promising areas for future NIH-sponsored research that would benefit the greatest need. Box S-1 provides the committee's Statement of Task.

## COMMITTEE'S APPROACH TO ADDRESSING ITS CHARGE

The committee formed to address NIH's task consisted of 13 experts in autoimmune diseases, immunology, epidemiology, environmental

### **BOX S-1** **Statement of Task**

The National Academies of Sciences, Engineering, and Medicine will convene an ad hoc committee to conduct a congressionally mandated study of NIH research on autoimmune diseases. The study will:

- Provide a general overview (with particular focus on NIH research efforts) of epidemiologic trends in autoimmune diseases.
- For common autoimmune diseases (including those that are overrepresented in women), evaluate the NIH research portfolio with particular attention to issues such as risk factors; diagnostic tools; barriers to diagnoses; treatments; and prospects for cures.
- Review NIH's research activities related to specific autoimmune diseases, the occurrence of multiple autoimmune diseases in individuals, and the interplay of autoimmune diseases and comorbidities.
- Assess trends in the focus of NIH research and address whether the trends are reflective of the changes in epidemiology as compared to other factors such as availability of research tools and technologies, and emerging biomedical knowledge and concepts.
- Identify barriers to NIH-sponsored research and research gaps for autoimmune diseases.
- Identify promising areas for future NIH-sponsored research for autoimmune diseases that would benefit the greatest need.
- Evaluate Institute and Center structure in support of NIH autoimmune disease research to identify where needs are met and where coordination could be enhanced.
- Produce and publish a final consensus committee report summarizing the committee's findings, conclusions, and recommendations. The report must address NIH accomplishments, challenges that NIH faces, as well as possible solutions to the challenges.

health, neurology, nephrology, gastroenterology, cardiology, psychiatry, rheumatology, disability, pediatrics, women's health, sex differences research, health disparities research, and research administration. The committee convened virtually 10 times, including 3 public sessions to gather information from individuals with expertise on topics and subjects of interest to the committee, including panels of representatives of NIH Institutes and Centers (ICs) and Offices; and experts on autoimmune diseases and autoimmune disease research from academia and disease-focused organizations.

Given the study timeframe, the committee chose a select number of autoimmune diseases to examine as it would be unable to examine a large set of diseases. Initially the committee cross-referenced diseases that two autoimmune disease organizations<sup>3</sup> agreed upon. To arrive at a final list, the committee considered autoimmune diseases that are identified in congressional language requesting this study; are overrepresented in women; may affect multiple systems and are associated with comorbidities; and that illustrate the spectrum of autoimmune diseases. A final consideration was the availability of data on NIH research funding for the disease, as the committee had determined that this could provide valuable information on the focus of NIH's autoimmune disease research portfolio.

The committee selected 11 diseases for special focus: Sjögren's disease, systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, psoriasis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), celiac disease, primary biliary cholangitis, multiple sclerosis, type 1 diabetes, and autoimmune thyroid disease (Graves' disease and Hashimoto's thyroiditis).

### **The Study Process and Information Gathering**

The committee first undertook a high-level examination of the 11 select diseases that illustrate the spectrum of autoimmune diseases, investigating each for epidemiology and impact, risk factors and etiology, diagnostic tools, treatments and prospects for cures, heterogeneity in presentation, animal models aiding in the understanding of the disease, as well as applicable research progress and gaps in answer to the statement of task.

With this context, the committee determined that the characteristics that distinguish autoimmune diseases from each other are important and provide valuable information about the pathogenesis of each disease.

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<sup>3</sup> The Autoimmune Association is a nonprofit organization focused on the impact of autoimmunity and the eradication of autoimmune diseases. The Autoimmune Registry, Inc., is a nonprofit organization serving as a hub for research, statistics, and patient data on autoimmune diseases.

However, the committee also recognized, and chose to highlight and discuss, the commonalities among autoimmune diseases.

The committee then undertook a review of the NIH research portfolio on autoimmune disease. The general framework for this review included, to the extent possible, reviewing a set of inputs (spending), activities (research conducted), and outputs (clinical trials, patents, and other indicators) of NIH's investment in autoimmune disease research.

The committee examined overall NIH spending for autoimmune disease research grants and projects and that of 13 ICs that contribute the most funding to autoimmune disease research. The committee examined congressional action regarding NIH autoimmune disease research, the different types of NIH-funded grants and awards, the process for reviewing and awarding grants, and the funding and operation of extramural and intramural programs. The committee also reviewed NIH-wide and individual-IC missions and strategic plans; autoimmune disease-related initiatives involving collaboration; and NIH approaches to coordinating research.

To examine the activities of the NIH-funded autoimmune disease research portfolio, the committee relied on two sources: NIH's Research, Condition, and Disease Categorization system (RCDC) and the NIH Research Portfolio Online Reporting Tools (RePORT) website. The committee analyzed data from fiscal year 2008, the first year for which data were available, through fiscal year 2020, the last year for which data were available at the time of analysis. All grants/projects categorized as being in the RCDC "autoimmune diseases" spending category for the designated period were assembled, and the resulting 8,470 grants constituted the committee's research database. The committee determined that certain types of grants merited particular attention in portfolio evaluation; investigator-initiated (R) grants, for example, are the bulk of NIH-funded research. The specified award types were analyzed by the committee in a variety of ways and according to NIH overall, individual ICs, and each disease of interest.

The statement of task directed the committee to evaluate the NIH research portfolio for issues such as risk factors, diagnostic tools, barriers to diagnoses, treatments, and prospects for cures. As reviewing 8,470 abstracts individually was not deemed feasible, the committee chose three approaches to the task, and the methodologies for these appear in Chapter 6 and Appendix H. The first applied topic modeling to identify the most common grant research topics and the fluctuation in these topics over time. For the second approach, the committee searched the abstract database to identify which other NIH RCDC spending categories co-occurred with the autoimmune disease-spending category; this analysis provided insight into themes in autoimmune disease research. For the

third method, committee members used their scientific knowledge and expertise to review a sample of more than 1,200 abstracts to assess the primary areas of research focus as identified in the statement of task.

The committee's approach to assessing the accomplishments, or outputs, of funded research on autoimmune disease included a high-level examination of clinical trial activity, bibliometric indicators, and patents. The methodologies are in Appendix G.

## CROSSCUTTING ISSUES IN AUTOIMMUNE DISEASES

Based on its review of the literature, the committee highlighted the characteristics that are common across autoimmune diseases because they provide valuable information about disease pathogenesis that could provide direction for more targeted research that might lead to strategies to prevent, delay, diagnose, treat, and cure disease. Considering autoimmune diseases as a “group” according to “common mechanisms of disease” might provide novel insights beyond those gained by focusing on the affected organ or system, or on individual diseases. Below are areas of research opportunity.

*Genetics.* Autoimmunity appears to require interaction between environmental factors and one or more genes. Many of the genes that confer susceptibility to autoimmune disease, and that the diseases share, regulate immune response; dysfunction of the immune response is critical to the development of autoimmune disease. Identifying the mechanisms that underlie genotype–phenotype associations will enable researchers to better target treatment.

*Environmental exposures.* Research supports a “second-hit” hypothesis—that a genetic profile requires an additional exposure event to become clinical illness. Among the exposures associated with autoimmune diseases are infectious agents and respirable silica. Defining the type and duration of exposures associated with disease for specific diseases and across diseases, as well as defining the permutations of genes and environmental exposures that lead to autoimmune diseases could benefit the field.

*Biomarkers.* Biomarkers such as cytokines and autoantibodies can be detected before clinical disease develops and an increase in pro-inflammatory cells, cytokines, and signaling pathways are implicated in disease development. Identifying traditional and novel biomarkers could enable disease prediction, which coupled with advances in therapeutic areas could possibly be used to delay or prevent disease before clinical disease develops, or modify disease outcomes.

*Sex.* Sex chromosomes, sex hormones, and the effects of environmental exposures on sex hormones appear to play a role in differences

between males and females in the occurrence and pathogenesis of autoimmune disease. Understanding this activity better could inform approaches to diagnosis and treatment.

*Autoimmune disease complications / coexisting autoimmune diseases.* Both are common, with some illnesses occurring across several autoimmune diseases. Examining the patterns could inform the understanding of pathophysiology and mechanistic pathways as well as approaches to patient care.

*Mechanistic pathways as therapeutic targets.* Mechanisms of immune-mediated damage that leads to the varied clinical phenotypes of different diseases may share common immune pathways. Identification of specific proinflammatory signaling pathways and their cytokines as pathogenic in autoimmune diseases has resulted in targeted therapeutics; some therapies have been shared across diseases. Discovery of further pathways that promote or inhibit autoimmune disease could inform drug development.

*Animal models.* Existing animal models have and can continue to help define common genetic and environmentally induced mechanisms. Development of models for diseases that do not have models and continued development of a variety of novel culture, animal, and other models to better answer questions posed by advances in translational research would benefit the field of autoimmune disease.

## **ANALYSIS OF INSTITUTE AND CENTER AND SPECIFIC AUTOIMMUNE DISEASE RESEARCH ACTIVITY**

In reviewing NIH's research portfolio on autoimmune diseases, the committee employed a general framework that considered the inputs (spending), activities (research conducted), and outputs (clinical trials, patents, and other indicators) of NIH's investment in autoimmune disease research. It is notable that spending on autoimmune diseases as a percentage of overall NIH obligations has remained at only 2.6 percent between 2013 and 2020. This is in marked contrast to increases seen in overall NIH obligations during the same period. In addition, the distribution of this funding for autoimmune diseases indicates that certain ICs dominate overall spending on research and training and the types of research activities funded.

An overview of the focus of the funded autoimmune research grants as requested by the statement of task was conducted using three different methodologies—artificial intelligence, NIH RCDC spending categories, and committee member judgement—yielding different levels of specificity. While there was some consistency in the focus areas identified among the three methods—the areas of pathophysiology of the immune

response, genetics, and treatment and therapy were common to all three methods—some methods highlighted other areas of focus more readily.

For accomplishments associated with funded research on autoimmune disease, the committee considered clinical trial activity, which represents translating research knowledge into interventions that influence health-related biomedical or behavioral outcomes; bibliometric indicators; and patents. With respect to clinical trials, there is a greater percentage of clinical trials from filing years 2008 to 2020 for such autoimmune diseases as type 1 diabetes, systemic lupus erythematosus, IBD, and rheumatoid arthritis, with a much smaller percentage seen for other autoimmune diseases. Further, results from bibliometric analyses indicate that the knowledge associated with existing research grants has been successfully disseminated to the research community through publications in well-regarded scientific journals. In terms of patent applications, filings occur primarily for some autoimmune diseases with far fewer filings for others. In general, findings related to research outputs suggest the need for a nuanced and in-depth examination of why progress via clinical trials and patent filings does not seem to have been made for certain autoimmune diseases.

Despite the generation of important information summarizing the autoimmune disease research enterprise, the committee encountered substantial challenges in making quantitative or qualitative judgements about the portfolio and the progress made to address the broad range of autoimmune diseases. In part, this is because a recent overarching strategic research plan with implementation goals and milestones does not exist, thus the committee was unable to discern concrete metrics against which progress could be assessed.

## **OPPORTUNITIES AND OPTIONS FOR ENHANCING AUTOIMMUNE DISEASE RESEARCH AT NIH**

The committee's formal review of the NIH autoimmune disease research portfolio confirms that much extraordinary work related to autoimmune disease has been undertaken and likely will continue. The committee also faced a daunting task given the evolving areas of autoimmunity and autoimmune disease, differing approaches to defining autoimmune disease, lack of consensus on what diseases they include, and a lack of epidemiologic data. The examination of the 11 diseases highlights the complexity of autoimmune diseases ranging from molecular mechanisms to individuals, families and populations affected, heterogeneity in presentation and evolution of the disease, and available treatments and responses to therapy. The committee agreed that the diseases' commonalities may provide additional and significant insights that can further

the development of patient care and therapies, and as such may offer the greatest opportunity for advancing the field.

The general framework for the review of the NIH autoimmune disease research portfolio includes inputs (funding, organizational structure and administrative processes, IC missions and strategies, collaborative initiatives, and methods of collaboration), activities (the kinds of research funded), and outputs or accomplishments.

Major barriers to NIH's ability to maximize outcomes of this research portfolio is the variation found in IC strategic plans regarding autoimmune diseases and most significantly, the absence of a research plan that spans all ICs to provide an overall strategic NIH plan for autoimmune diseases. Absent the latter, NIH lacks a comprehensive, transparent, and strategic approach to how it plans and evaluates progress made on autoimmune disease research.

The committee determined that five essential elements are necessary for rapid advancement and improvement in autoimmune disease research:

1. Strategic research planning to set priorities
2. An emphasis on coordinating across ICs and enhancing collaborative research given the crosscutting nature of autoimmune diseases
3. An orientation toward innovation
4. A focus on evaluating the autoimmune research portfolio in order to determine progress made across NIH
5. Resources to support planning, collaboration, and innovation

While the committee recognizes that the diffuse and investigator-initiated nature of NIH research and of autoimmune disease research in particular has many well-described and accepted advantages, NIH does not optimally promote these five elements.

Identifying gaps and opportunities can be achieved by a relatively independent, structured, and ongoing examination of the research conducted. This can then inform planning for how to most successfully address those gaps and opportunities, which would also benefit from a detailed but not prescriptive strategic plan. Neither a rigorous evaluation nor strategic planning currently occurs in an overarching, sustained, and resourced fashion. There currently is no overarching strategic plan guiding research activities and IC collaboration on autoimmune research activities.

The committee identified an opportunity not just for filling gaps that may fall between the work of diverse ICs but also for capturing and leveraging an understanding of the crosscutting nature of autoimmune

diseases, including their underlying common disease mechanisms, risk factors, and shared concomitant conditions. The committee believes that the emerging and evolving science now makes those connections more achievable than ever before. Such information could be building blocks for, and could accelerate innovative progress toward prevention, early diagnosis, treatment, and cure.

Some of this work can advance without the infusion of major new resources. However the committee believes that any centralized entity, to be effective, will require new resources; and that the broader and better research enterprise on autoimmune disease has a greater potential to bring relief to patients and their families.

The committee considered five options for enhancing autoimmune disease research and resulting outcomes. These included (1) increased funding for autoimmune disease research; (2a) coordination through revitalization of the NIH Autoimmune Disease Coordinating Committee; (2b) coordination through creation of a U.S. Department of Health and Human Services Autoimmune Disease Coordinating Committee; (3) development of a congressionally mandated national autoimmune diseases/autoimmunity research plan; (4) creation of a new National Institute of Autoimmune Disease and Autoimmunity Research; and (5) creation of an Office of Autoimmune Disease/Autoimmunity Research within the Office of the Director of NIH. The pros and cons, costs, and feasibility of each option are discussed in Chapter 7.

The committee found that the best option for addressing these challenges and opportunities would be the creation of an Office of Autoimmune Disease/Autoimmunity Research within the Office of the Director of NIH. It found significant merit in this option, provided the option is pursued in a way in which it is likely to succeed.

Such an Office would be positioned to respond to the committee's concerns by:

- Facilitating cross-NIH multidisciplinary collaboration and stimulating innovation around autoimmune disease research
- Engaging in priority setting, strategic planning, and implementation
- Budgeting for and allocating available research funds in alignment with the strategic plan
- Managing and evaluating research efforts
- Communicating with key stakeholders
- Providing visible leadership on autoimmune disease research.

This option is not a new one and was proposed in a bill advanced by then Senator Joe Biden in 1999.

Realistically, as governmental units at NIH and elsewhere persuasively argue to the Congress, the impact of a research organization is likely

to be correlated with the extent to which it owns and controls resources. This is particularly true in the case of new entities advising on and negotiating the activities of multiple actors who are already resourced. Given this, the committee considered two configurations of this Office.

In the first, the Office would have its own research budget and it would substantially control certain key budgetary decisions about autoimmune disease research activities conducted elsewhere in NIH. In the second configuration, while the Office would have certain responsibilities, it would receive only modest or limited resources or authority to carry them out. Current Offices have budgets that range widely, which can affect an Office's ability to fund research, and most Offices are permitted to fund grants only in collaboration with an IC. The ability of the Office of AIDS Research to allocate congressionally appropriated funds for AIDS research is unusual. The committee recommends the former, fully recognizing that budgetary control is among the most sensitive issues within any organization. The committee recognizes that some middle ground might need to be struck.

Success will also depend on tailoring the Office to specific and manageable objectives. Further, a successful crosscutting Office needs the capacity to suggest and advance creative new scientific approaches, partners, and paradigms. While effective offices recognize the importance of living within institutional cultures and constraints, they can still suggest and direct new ways of doing business that others may not see, have the time or expertise to consider, or the resources to pursue. This, in the view of the committee, is how a new Office of Autoimmune Disease/Autoimmunity Research within the Office of the NIH Director would provide its greatest value.

As noted above, the committee believes that successful implementation of any option will depend on careful attention to a variety of critical success factors in addition to budget considerations. Simply put, the committee believes that no new office is preferable to one that is not substantive, serious, supported, well defined, and well resourced. NIH is an institution with world-class expertise, billions of dollars in resources, and extraordinarily high standards. No one benefits when a new organization is created at NIH that does not meet those standards.

With these provisos, the committee believes that a well-configured Office of Autoimmune Disease/Autoimmunity Research could be an essential ingredient in further stimulating promising and impactful autoimmune disease and autoimmunity research at NIH that can be translated into clinical practices that will prevent autoimmune disease or improve the lives of those living with autoimmune disease. The responsibilities the committee envisions for the Office appear in Box S-2.

**BOX S-2**  
**Duties of the Office as Envisioned by Committee**

- A. The Office would devise a process for and lead the collaborative development of a *Strategic Plan* to address opportunities and gaps in scientific knowledge. This would result in an *NIH Strategic Plan for Autoimmune Disease and Autoimmunity Related Research*. The plan would:
1. Establish both a high-level blueprint and a more detailed research agenda.
  2. Set both high-level national priorities and detailed disease-specific and cross-cutting priorities.
  3. Describe a detailed research program and implementation plan for carrying out that agenda.
  4. Work with ICs to identify and promote research opportunities that align with strategic plan goals (e.g., developing solicited requests for applications (RFAs) for crosscutting research grants, promoting Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs grants).
  5. Address autoimmune disease research workforce and training issues, including diversity of the workforce.
  6. Provide metrics for evaluating progress and a process for applying those metrics.
  7. Examine scientific and organizational barriers to breakthroughs and potential solutions.

In developing and implementing the strategic plan, the Office would actively seek the collaboration and engagement of IC intramural and extramural investigators and other stakeholders. This outreach would serve to catalyze innovation and identify emerging areas of research opportunity. Strengthening outreach could also inform funding for other important research priorities undertaken by various ICs.

In support of strategic planning, the Office, in collaboration with ICs and other stakeholders, should develop a consensus vocabulary that includes both clinically defined autoimmune diseases and autoimmune mechanisms and a list of autoimmune diseases. Such a definition and list of diseases is critical to improve research and data collection, and guide patient care and coordinate communication. Periodic reassessment of the definition and listing of autoimmune diseases should be undertaken based upon emerging data.

- B. The Office would ensure that funds are invested in the areas of highest scientific priority. The Office would:
1. Engage in developing detailed autoimmune disease research budgets.
  2. Set budgetary priorities and attempt to align available dollars.
  3. With its own resources fund certain activities including those that are cross-cutting; high risk/reward; relevant to special populations; and related to workforce development.

- C. The Office would provide scientific coordination and management of the research program. This would include:
  1. Serving as a focal point for external parties seeking information or providing input on autoimmune disease research opportunities at NIH.
  2. Serving as a convener for emerging and crosscutting science on autoimmune disease. Collaborating with organizations focused on persons-centered research like the Patient-Centered Outcomes Research Institute and other stakeholders—industry, disease organizations, patient advocacy, and patients and their families—in priority setting and research design.
  3. Stimulating novel approaches to autoimmune disease research.
  4. Leveraging existing efforts and develop synergies across multiple ICs and scientific disciplines.
  5. Coordinating with the Center for Scientific Review to review assignment guidelines to ensure that autoimmune diseases grants are assigned to the appropriate study sections with optimal representation of experts and expertise, including expertise for reviewing basic science (i.e., tissue culture, animal, translational) and human studies, and evaluate assignment guidelines on an ongoing basis.
  6. Coordinating existing autoimmune disease data-collection systems and bio-repository resources across NIH; creating a database of such resources to facilitate research collaboration; and coordinating with external databases that may have useful data (e.g., the VA Million Veterans Program, the UK Biobank, and industry biorepositories).
  7. Coordinating autoimmune disease research across other HHS agencies and other federal agencies (e.g., Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Food and Drug Administration) to promote cohesion in efforts to advance generation of knowledge and care delivery for autoimmune disease.
- D. The Office would conduct or contract for evaluations of ongoing efforts.
- E. The Office would produce annual reports on the progress made on autoimmune disease research activities for Congress. Annual congressional reports can provide key information on priorities and outcomes to enable policymakers to assess the level of funding for autoimmune disease research. Others who could benefit from such information are key stakeholders in the autoimmune research enterprise and members of the public.
- F. Building on this report and other relevant reviews, the Office would lead the development of an enhanced information system for autoimmune disease research. The committee's efforts revealed challenges researchers and policymakers may face in easily accessing, synthesizing, and analyzing relevant research opportunities and results. The committee believes that, consistent with NIH's existing and excellent information systems, more can be done to allow researchers ready but refined access to research opportunities and ongoing research efforts.

The committee's recommendations follow, the introduction for Recommendation 1 having been provided.

**Recommendation 1: The Director of the National Institutes of Health should create an Office of Autoimmune Disease/Autoimmunity Research within the Office of the Director.**

Acknowledging that creating an Office of Autoimmune Disease/Autoimmunity Research may take some time, the committee makes two specific recommendations related to data collection that could be implemented independent of the Office by ICs, one independently and the other in collaboration with other ICs. First, progress on autoimmune disease requires substantially more sophisticated and refined epidemiology on the individual and aggregate burden of autoimmune disease. The extant knowledge base is growing, but there are important gaps, including incidence and prevalence trends, comprehensive evaluations of the risk factors and the burden (including direct and indirect costs) of these diseases, the impact on different populations, the trajectory of these diseases from the period before disease manifests through the life course, and the impact of specific treatments and interventions.

The committee found a lack of long-term (20 years or more) population-based epidemiology studies on autoimmune disease. Such studies would allow for assessing trends, identifying differences among population subgroups, and determining the prevalence and incidence of under-researched autoimmune diseases and conditions, such as celiac disease. The National Cancer Institute's Surveillance, Epidemiology, and End Results Program, which provides information on cancer incidence and survival in the United States, is a model for such studies already existing at NIH.

**Recommendation 2: The National Institutes of Health should establish long-term systems to collect and ensure optimum usability of population-based surveillance and epidemiological data (e.g., incidence, prevalence) on autoimmune diseases and measures of autoimmunity (e.g., autoantibodies, inflammation) and support the optimization of existing data sources.**

The committee also found that few studies exist that are able to provide information on the long-term progression of autoimmune disease beginning in the period before disease manifests through the life course. Such studies would allow for a greater understanding of the heterogeneity of disease expression and changes with time and over various

life stages. Such studies could be designed to address wide variety of disease outcomes and health effects.

Establishing population cohorts is critical for studying mechanisms leading to autoimmune diseases. Early life exposures and timing of these exposures influence health at different life stages at a population and individual patient level. Autoimmune diseases are long-lasting heterogeneous conditions for which manifestations and comorbidities change over time. It is essential to support long-term (10–20+ years) patient cohort studies. Such studies would provide understanding of opportunities for developing clinical treatments and behavioral interventions.

**Recommendation 3: The National Institutes of Health should support the development of population cohorts that extend from the period before disease manifests to the development of symptoms and disease, and should support patient cohorts that will allow the examination of the progression, coexisting morbidities, and long-term (20+ years) outcomes of autoimmune diseases. Data collection should include, but need not be limited to:**

- **Genome-wide association**
- **Environmental and occupational exposures such as respirable silica, vitamin D and iodine, viruses, and smoking**
- **Autoantibody, cytokine, and T cell assays, particularly in new-onset disease**
- **Response to therapeutic interventions, including timing of treatment (e.g., to assess whether early treatments prevent disease progression)**
- **Development of co-occurring autoimmune diseases**

Finally, to address the research gaps outlined throughout this report, a comprehensive national research agenda for autoimmune diseases is required. Achieving this objective will require coordination and collaboration among researchers, research groups, and stakeholders as well as the dedicated pursuit of research that defines autoantibodies that predict and diagnose autoimmune diseases; identifies common mechanisms in inflammation; determines gene–environment interactions within and across autoimmune diseases; examines the role of environmental exposures on autoimmune diseases; elucidates disparities and their determinants; determines the impact of comorbidities and complications of autoimmune diseases on clinical outcomes, functional outcomes, quality of life, and health care utilization; and explores the effect of interventions to mitigate impact of comorbidities and complications for patients with autoimmune disease across the lifespan.

**Recommendation 4:** The National Institutes of Health should provide funding and support for a national research agenda that addresses key gaps identified by the committee. Prioritized research streams should include, but need not be limited to, clinical and basic research that addresses the research streams below.

- Dissect heterogeneity across and within autoimmune diseases to decipher common and disease-specific pathogenic mechanisms
- Study rare autoimmune diseases and develop supporting animal models
- Define autoantibodies and other biomarkers that can diagnose and predict the initiation and progression of autoimmune diseases
- Determine the biologic functions of genetic variants and gene-environment interactions within and across autoimmune diseases using novel, cutting-edge technologies
- Examine the role of environmental exposures and social determinants of health in autoimmune diseases across the lifespan
- Determine the impact of coexisting morbidities, including co-occurring autoimmune diseases and complications of autoimmune diseases, across the lifespan, and develop and evaluate interventions to improve patient outcomes.
- Foster research to advance health equity for all autoimmune disease patients

The committee provides detailed subheadings for these research areas in Chapter 7.

## CONCLUSION

The quantity and quality of the research NIH conducts on autoimmune diseases is impressive. The committee believes that a strategic plan for all NIH autoimmune disease research and a well-configured and well-funded Office to support the coordination and collaboration of all ICs that can play a role in advancing the field represent an opportunity for NIH both to optimize its significant resources and to maximize the ground covered by the research it conducts.

# Introduction

Autoimmune diseases occur when the body's immune system, which normally defends the body against disease and infection, malfunctions and mistakenly attacks healthy cells, tissues, and organs (NIEHS, 2021). These attacks can affect any part of the body, and damage may target a specific organ system or be systemic (Fridkis-Hareli, 2008). For some diseases, diagnosis can be problematic; people can experience symptoms and accrue tissue damage for years and consult multiple physicians before receiving a correct diagnosis (Arbuckle et al., 2003; Calabrese et al., 2021; Dall'Era, 2013). Pain is a common symptom, and nerve dysfunction can amplify pain sensations (Mifflin and Kerr, 2017). People with autoimmune diseases commonly develop more than one autoimmune disease (Cojocaru et al., 2010; Rojas-Villarraga et al., 2012), and they can be at increased risk of developing cancer (Franks and Slansky, 2012) and cardiovascular disease (Williams et al., 2019) among other comorbidities and complications. Autoimmune diseases are chronic and lifelong and can cause significant physical and psychosocial impairment, impeding activities of daily living, productivity, and quality of life. In children, autoimmune diseases can cause irreversible organ damage at an early age and adversely affect growth and development, with lasting effects into adulthood (Amaro and Chiarelli, 2020; Cirillo et al., 2017; Groot et al., 2019; Heshin-Bekenstein et al., 2018; Lim et al., 2013, 2017; Mauras et al., 2021; Mitchell, 2017; Ruano et al., 2018). Autoimmune disease can also be fatal; uncontrolled type 1 diabetes is well-known to be life-threatening (Reno et al., 2018), a 2018 study determined systemic lupus erythematosus to be a leading cause of

death in young females in the United States (Yen and Singh, 2018), and autoimmune diseases as a group rank among the 10 leading causes of death for females (Thomas et al., 2010; Walsh and Rau, 2000). There are no known cures for autoimmune diseases.

There are limited data on the incidence and prevalence of autoimmune diseases. In 2005, the National Institutes of Health (NIH) Autoimmune Diseases Coordinating Committee (ADCC)<sup>1</sup> estimated that autoimmune diseases affect 14.7 to 23.5 million people in the United States (ADCC, 2005). More recent epidemiologic data are inadequate to provide an updated estimate of the U.S. prevalence of autoimmune diseases, but the number is likely higher given the increase in the U.S. population (United States Census Bureau, 2021) and the prevalence of some autoimmune diseases and autoantibodies appears to be growing (Dinse et al., 2020; Mayer-Davis et al., 2017; Shivashankar et al., 2017). The personal and societal costs of autoimmune diseases are substantial but difficult to estimate overall, because costs are attributed mostly to specific diagnoses and because calculations of acute care costs, medications, hospitalizations, and annual or lifetime costs, for example, are not standardized across autoimmune diseases (AARDA and NCAPG, 2011).

NIH, the U.S. federal agency primarily responsible for sponsoring and conducting biomedical research, supports research on autoimmune disease.<sup>2</sup> NIH's stated mission is to "seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability" (NIH, 2017). The agency conducts its mission and goals through a complex and multidisciplinary structure of 27 Institutes and Centers (ICs), each focusing on different areas of biomedical research. The Office of the Director sets policies and coordinates the activities of the ICs. Autoimmune disease research activities occur across the ICs through both extramural and intramural research activities. In fiscal year 2020, NIH's budget obligations<sup>3</sup> were approximately \$41.5 billion, of which NIH spent \$1.1

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<sup>1</sup> NIH established the ADCC in 1998 in response to congressional encouragement to facilitate coordination of autoimmune disease research across NIH, federal agencies, professional societies, and patient and advocacy organizations (NIAID, 2021).

<sup>2</sup> NIH is one of the 11 operating divisions in the U.S. Department of Health and Human Services (HHS, 2022). The other 10 operating divisions are Administration for Children and Families (ACF), Administration for Community Living (ACL), Agency for Healthcare Research and Quality (AHRQ), Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), Indian Health Service (IHS), and Substance Abuse and Mental Health Services Administration (SAMHSA).

<sup>3</sup> Actual total obligations.

billion, or 2.6 percent of the NIH obligations, supporting autoimmune disease research (NIH, 2020, 2021).

In language supporting the Further Consolidated Appropriations Act, 2020,<sup>4</sup> Congress noted that autoimmune diseases affect an estimated 5 to 7 percent of Americans; that these diseases are more common in women than men; and that many women with one autoimmune disease have a second autoimmune disease or other condition. That language also stated that “there is no single office within National Institutes of Health tasked with coordinating research across the agency or examining the complex interplay among these diseases and conditions,” and it called for NIH to contract with the National Academies of Sciences, Engineering, and Medicine (National Academies) to identify and review NIH’s research efforts in this broad area. In response, the National Academies convened the Committee for the Assessment of NIH Research on Autoimmune Diseases (the committee) to respond to this request. The 13-member interdisciplinary committee consisted of experts in autoimmune diseases, immunology, epidemiology, environmental health, neurology, nephrology, gastroenterology, cardiology, psychiatry, rheumatology, disability, pediatrics, women’s health, sex differences research, health disparities research, and research administration. One member of the committee has had multiple sclerosis for years, providing insight into the lived experience of having an autoimmune disease. More information about the committee members can be found in Appendix A.

### Charge to the Committee

The Statement of Task guiding this study charged the committee to assess NIH research activities on autoimmune diseases with a particular emphasis on the risk factors, diagnostic tools, barriers to diagnoses, treatments, and prospects for cures. The committee’s task also included considering the occurrence of multiple autoimmune diseases and the interplay of the diseases with comorbidities, as well as identifying barriers to NIH-sponsored research, research gaps, and promising areas for future NIH-sponsored research that would benefit the greatest need. Box 1-1 provides the committee’s Statement of Task.

### Committee’s Approach

For the purpose of this report, the committee’s review of NIH autoimmune disease research funding focused on a select number of autoimmune

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<sup>4</sup> Further Consolidated Appropriations Act, H.R.1865, 116th Cong., 1st sess., Congressional Record 165, no. 204, daily ed. (December 17, 2019): H11071.

### **BOX 1-1** **Statement of Task**

The National Academies of Sciences, Engineering, and Medicine will convene an ad hoc committee to conduct a congressionally mandated study of NIH research on autoimmune diseases. The study will:

- Provide a general overview (with particular focus on NIH research efforts) of epidemiologic trends in autoimmune diseases.
- For common autoimmune diseases (including those that are overrepresented in women), evaluate the NIH research portfolio with particular attention to issues such as risk factors; diagnostic tools; barriers to diagnoses; treatments; and prospects for cures.
- Review NIH's research activities related to specific autoimmune diseases, the occurrence of multiple autoimmune diseases in individuals, and the interplay of autoimmune diseases and comorbidities.
- Assess trends in the focus of NIH research and address whether the trends are reflective of the changes in epidemiology as compared to other factors such as availability of research tools and technologies, and emerging biomedical knowledge and concepts.
- Identify barriers to NIH-sponsored research and research gaps for autoimmune diseases.
- Identify promising areas for future NIH-sponsored research for autoimmune diseases that would benefit the greatest need.
- Evaluate Institute and Center structure in support of NIH autoimmune disease research to identify where needs are met and where coordination could be enhanced.
- Produce and publish a final consensus committee report summarizing the committee's findings, conclusions, and recommendations. The report must address NIH accomplishments, challenges that NIH faces, as well as possible solutions to the challenges.

conditions over a select period of time. The committee notes that there is neither a consensus definition of autoimmune disease, nor a standard list of autoimmune diseases, though the National Institute of Allergy and Infectious Diseases (NIAID) identifies more than 80 autoimmune diseases (NIAID, 2017). In addition, the Autoimmune Registry<sup>5</sup> and the Autoimmune Association (formerly named American Autoimmune Related

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<sup>5</sup> The Autoimmune Registry, Inc., is a nonprofit organization that serves as a hub for research, statistics, and patient data on all autoimmune disease (Autoimmune Registry Inc., 2021).

Diseases Association, or AARDA)<sup>6</sup> compiled two longer lists of autoimmune diseases that include 147 and 150 diseases, respectively (Autoimmune Association, 2021b; Autoimmune Registry Inc., 2020). Appendix B lists the diseases the Autoimmune Association identifies as autoimmune diseases. The committee acknowledged that given the timeframe it had to conduct its work, it would be unable to examine a large set of autoimmune diseases. As an initial step in selecting a set of diseases, the committee cross-referenced the Autoimmune Association list of diseases with the list of diseases that the Autoimmune Registry designates as having “strong” evidence for being autoimmune diseases. The committee deemed the resulting list to be a reasonable starting point from which to choose.

### *Autoimmune Diseases of Focus*

A number of factors contributed to the committee’s selection of autoimmune diseases. Box 1-2 lists these factors, and Table 1-1 lists the diseases the committee selected.

The committee acknowledges that there are autoimmune diseases that are more rare than the diseases it selected for special focus, but the committee believes that including rare diseases could have diminished its ability to answer the questions with which it had been tasked.

#### **BOX 1-2** **Factors Considered in Selecting Diseases for Special Focus**

- Autoimmune diseases identified in Congressional Record H11061-01, 2019.
- Diseases overrepresented in women.
- Diseases that may affect multiple systems and are associated with comorbidities.<sup>1</sup>
- Diseases that illustrate the spectrum of autoimmune disease.
- Availability of NIH data on research funding for the disease.

<sup>1</sup> More granular definitions of coexisting disease (comorbidity, complication, co-occurring autoimmune disease, and overlapping autoimmune disease) are provided in Chapter 2.

<sup>6</sup> The Autoimmune Association (previously known as the American Association of Autoimmune Related Disorders [AARDA]) is a nonprofit organization focused on the eradication of autoimmune diseases and impact of autoimmunity (Autoimmune Association, 2021a).

**TABLE 1-1** Disease Selection Considerations

Prominent in Women	Included in Further Consolidated Appropriations Act, 2020 <sup>a</sup>	RCDC <sup>b</sup> Spending Category	Additional Considerations
Sjögren's Disease	X		Comorbid with other autoimmune conditions; relatively older onset; difficult to diagnose
Systemic Lupus Erythematosus	X	X	X
Antiphospholipid Syndrome	X		Closely related to systemic lupus erythematosus; particularly prominent for pregnancy risk
Rheumatoid Arthritis	X	X	X
Psoriasis			X
Inflammatory Bowel Disease <sup>c</sup>	X	X	X
Celiac Disease	X	X	
Primary Biliary Cholangitis	X		Population disparities
Multiple Sclerosis	X	X	X
Type 1 Diabetes		X	Acute mortality risk; relatively young onset
Autoimmune Thyroid Disease	X		High prevalence

<sup>a</sup> Further Consolidated Appropriations Act, H.R.1865, 116th Cong., 1st sess., Congressional Record 165, no. 204, daily ed. (December 17, 2019): H11071.

<sup>b</sup> RCDC is the NIH Research, Condition, and Disease Categorization system.

<sup>c</sup> Includes Crohn's disease and ulcerative colitis.

### *Autoimmune Diseases Identified in Congressional Record and Overrepresentation of Women*

The language supporting the call for the National Academies study specifically noted the following autoimmune diseases: rheumatoid arthritis, multiple sclerosis, lupus, celiac disease, inflammatory bowel disease, and type 1 diabetes. The congressional language also included a reference to the 2010 National Academies study *Women's Health Research: Progress, Pitfalls, and Promise* that identified autoimmune conditions as "the leading cause of morbidity in women, and they affect women's quality of life greatly" (IOM, 2010). The Statement of Task does not direct the committee to focus exclusively on women's health, but it does direct the committee to examine "common autoimmune diseases (including those overrepresented in women)." The committee decided to include the six diseases identified in the congressional language along with Sjögren's disease (sometimes called Sjögren's syndrome), psoriasis, antiphospholipid syndrome, primary biliary cholangitis, and autoimmune thyroid disease, each of which also affects more women than men. The committee notes that while many autoimmune diseases do occur predominantly in women, multiple other patterns occur across autoimmune diseases in relation to age, sex, race and ethnicity, and social determinants. Variations also exist in other dimensions of autoimmune disease, including progression of disease and outcomes.

### *Diseases That May Encompass Multiple Systems and Comorbidities.*

Unlike many other illnesses, autoimmune diseases affect multiple organ systems (e.g., skin, kidney, lung, joints, and brain), sometimes leading to different manifestations with different names. Many autoimmune diseases overlap; for example, features of Sjögren's disease or Hashimoto's thyroiditis (also called Hashimoto's disease) often accompany rheumatoid arthritis, systemic lupus erythematosus, and related illnesses. There is little consensus whether such patients have one or several autoimmune diseases.

### *Diseases That Collectively Illustrate the Spectrum of Autoimmune Diseases*

The committee sought to select diseases that could illustrate the spectrum of autoimmune disease, which is diverse in organ systems affected, disease course, patient population, time of onset, and severity, among other factors. For example, type 1 diabetes is a disease that most often arises in children, adolescents, and young adults, while systemic lupus erythematosus usually first manifests in young adulthood, and multiple

**BOX 1-3**

**Sjögren's Disease Highlights Features and Complexities Common in Autoimmune Disease**

- Most common in women
- Can be diagnosed at different ages (Ramos-Casals et al., 2021)
- May affect nearly any organ system
- May involve systemic features and profound pain and fatigue
- Associated with complications during pregnancy
- Associated with increased risk of developing cancer (Vivino et al., 2019)
- May lead to disability
- Autoimmune response is complex and progresses over years
- Commonly co-occurs with other autoimmune diseases

sclerosis during midlife; however, each of these illnesses can occur at any age (Bar-Or, 2016; Cartee et al., 2016; Dall'Era et al., 2017; Lim et al., 2014; Somers et al., 2014).

*Availability of NIH Data on Research Spending for Autoimmune Disease*

The committee determined that NIH funding data would provide valuable information on the focus of NIH's autoimmune disease research portfolio. The committee relied on two sources for that information: NIH's Research, Condition, and Disease Categorization system (RCDC) and the NIH Research Portfolio Online Reporting Tools (RePORT) website.<sup>7</sup> RCDC provides an overview of NIH funding, including a broad category for "autoimmune diseases" (referred to as "parent category") and seven subcategories (referred to as "child categories") of autoimmune diseases.<sup>8</sup> These "child categories" provide added transparency to the public on funding for specific autoimmune diseases. The RePORT website provides public access to a variety of reporting tools, reports, data, and analyses of NIH research activities. One of the tools available on the RePORT website is the RePORTER module that allows users to search a repository of

<sup>7</sup> The NIH Reform Act of 2006 encouraged NIH to prioritize consistency and transparency in the reporting of its funded research. Implemented in 2008, the RCDC system uses sophisticated text data mining (categorizing and clustering using words and multiword phrases) in conjunction with NIH-wide definitions used to match projects to specific funding categories (ERA, 2019; NIH, 2020).

<sup>8</sup> The child categories of the parent category "autoimmune disease" are inflammatory bowel disease (includes Crohn's disease), lupus, multiple sclerosis, rheumatoid arthritis, scleroderma, psoriasis, myasthenia gravis, and all other autoimmune disease research at NIH (McNamara, 2021).

NIH-funded intramural and extramural research grants by RCDC spending categories and to access publications and patents resulting from NIH funding.

The committee analyzed data from fiscal year 2008 to 2020, the last year for which data were available at the time of analysis. To expedite data analysis, an external contractor with experience using NIH RePORT tools provided assistance in reviewing data on publications, clinical trials, and patents resulting directly from NIH autoimmune funded work. Appendix G describes the methods used to perform RePORTER analyses.

To aid in assessing the 2008–2020 autoimmune disease research portfolio for the appearance of research topic patterns and trends, an external consultant used an artificial intelligence program to apply topic modeling, a form of statistical modeling, to the data. Appendix H describes the methodology. The committee used PICO Portal, a publications management tool, to review sampled abstracts of funded research grants. The rationale and methods for sampling and for the committee’s review can be found in Chapter 6.

### **The Study Process and Information Gathering**

The committee convened virtually 10 times, and between these meetings, small groups of committee members participated in virtual meetings or conference calls to advance their work. The committee held three public sessions to gather information from individuals with expertise on topics and subjects of interest to the committee, including panels of representatives of NIH ICs and Offices; experts on autoimmune diseases and autoimmune disease research from academia and disease-focused organizations; and individuals with autoimmune disease who provided insights into their lived experiences. The committee held public sessions during its first three meetings; Appendix C lists the agendas and presentation topics.

In addition to information provided by invited speakers, at the instruction of the committee, National Academies staff interviewed NIH representatives to gather information on approaches NIH uses to advance collaboration on and coordination of autoimmune disease research, both in and outside NIH. The committee also obtained information from NIH via direct request to the relevant Offices or ICs. These inquiries sought background and details on issues raised during presentations and committee deliberations and on the NIH RePORT tools. All presentations and responses to information requests are available in the public access file for the project.<sup>9</sup> Information on the missions, priorities, programs,

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<sup>9</sup> Available at <https://www8.nationalacademies.org/pa/managerequest.aspx?key=HMD-BPH-20-11> (accessed April 15, 2022).

collaborations, and funding processes of NIH ICs came from a review of NIH websites supplemented with information presented by representatives of ICs and Offices of NIH at the committee's public sessions.

The committee, aided by National Academies staff, conducted literature reviews to obtain information on the incidence and prevalence of autoimmune disease and other factors, such as associated comorbidities. The committee gave preference to U.S. data when they were appropriately rigorous and inclusive, but when U.S. data focused on small populations or lacked rigor, the committee used data from other countries in which health care systems and registries better enable the collection of data.

### Organization of the Report

This report is organized into two parts and seven chapters. Part I: Introduction, Background on Autoimmune Diseases, Select Autoimmune Diseases, and Crosscutting Issues (Chapters 1–4) and Part II: NIH Autoimmune Disease Research Efforts and Analysis of Autoimmune Disease Research Funding (Chapters 5–7). In addition to this Introduction (Chapter 1), which provides an overview of the origin, purpose, and organization of the report, Chapter 2 (Background on Autoimmune Disease) provides information on how the autoimmune diseases are defined and an overview of the occurrence and course of autoimmune diseases. Chapter 3 (Select Autoimmune Diseases) provides more information specific to the autoimmune diseases that the committee selected to focus on. The overview in Chapter 3 begins with a discussion of Sjögren's disease because the disease illustrates many of the features and complexities common to autoimmune diseases, some of which are listed in Box 1-3. After Sjögren's disease, Chapter 3 discusses other systemic autoimmune rheumatic diseases, followed by autoimmune diseases that affect a specific tissue or organ system, including skin, gastrointestinal system, central nervous system, and endocrine system.

Chapter 4 (Crosscutting Issues in Autoimmune Disease) discusses a number of issues that have implications for autoimmune disease research activities. Chapter 5 provides an overview of NIH autoimmune disease research efforts, and Chapter 6 provides an analysis of funding for the autoimmune diseases the committee focused on. Chapter 7 identifies opportunities for enhancing autoimmune disease research at NIH.

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# 2

## Background on Autoimmune Diseases

### DEFINING AUTOIMMUNE DISEASES

The immune system comprises cellular, chemical, and soluble protein components that together protect the body against foreign substances, including infectious agents and tumor cells, while not responding to molecules that signify “self” (Chaplin, 2010; Marshall et al., 2018). Autoimmunity arises when the immune system fails to distinguish self from non-self at the level of specific regions of cell surface molecules, or epitopes, recognized by two of the major effectors of the immune system: B cells, which produce antibodies, and T cells.<sup>1</sup> Autoimmune disease by definition, then, is autoimmunity that results over time in a pathological outcome with self-reactive, or autoreactive, T cells and autoantibodies causing tissue damage (Brent et al., 2007; Johns Hopkins University, 2022; Rose and Bona, 1993; Rosenblum et al., 2015). In 1993, Rose and Bona reevaluated Witebsky’s postulates<sup>2</sup> defining autoimmune disease, and proposed three levels of evidence to establish that a human disease is autoimmune in origin, including direct evidence by transfer of disease with pathogenic autoantibody or autoreactive T cells, indirect evidence

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<sup>1</sup> In recent years, evidence of innate immune mechanisms that recognize and respond to damage to self-tissues has blurred self/non-self distinctions (Abbas et al., 2004; Rose and Mackay, 2014).

<sup>2</sup> The postulates required that “an autoimmune response be recognized in the form of an autoantibody or cell-mediated immunity; that the corresponding antigen be identified, and that an analogous autoimmune response be induced in an experimental animal. Finally, the immunized animal must also develop a similar disease” (Rose and Bona, 1993).

based on reproduction of the autoimmune disease in an animal model, and circumstantial evidence from clinical data (Rose and Bona, 1993).

The terms autoimmunity and autoimmune disease originated in the 1950s, but in 1999 the term “autoinflammatory disease” emerged, which emphasizes the critical role of the innate immune system—the quickly reacting, nonspecific component of the immune system—in chronic inflammatory diseases where autoantibodies and autoreactive T cells play less of a role in mediating pathology (Abbas et al., 2004; Brent et al., 2007; Masters et al., 2009; Rose and Mackay, 2014; Stoffels and Simon, 2014). Autoinflammatory diseases are broadly considered by the scientific community to be those conditions driven predominantly by innate immune cells, such as macrophages, mediating systemic inflammation and self-tissue pathology, whereas autoimmune diseases occur when adaptive immune cells—T cells and B cells—targeting self-antigens are the dominant response causing inflammation and tissue damage.

Some diseases are clearly autoinflammatory in nature, such as familial Mediterranean fever, Behcet’s disease, and Still’s disease (Ciccarelli et al., 2014). Others are clearly autoimmune disorders, including multiple sclerosis and systemic lupus erythematosus (SLE). However, distinguishing between autoimmune and autoinflammatory disease can be difficult because activation of the innate immune system is a prerequisite for triggering an adaptive immune response (Iwasaki and Medzhitov, 2015). In fact, for most immune-mediated inflammatory diseases such as atherosclerosis, and prototypical autoimmune diseases such as multiple sclerosis, the innate and adaptive immune systems both play a role in promoting disease, leading to the notion of a spectrum or continuum of autoinflammatory-autoimmune diseases (Hedrich, 2016; McGonagle and McDermott, 2006).

Moreover, research is showing that diseases that medical science has not historically considered to be autoimmune diseases, such as atherosclerosis, Parkinson’s disease, and cancer, have autoimmune mechanisms such as autoantibodies (de Jonge et al., 2021) and autoreactive T and B cells that contribute to the pathogenesis of disease (Ketelhuth and Hansson, 2016; Lindestam Arlehamn et al., 2020). Research on Parkinson’s disease, for example, has revealed that T cell reactivity, which prompts an attack on brain cells, is associated with early and even preclinical disease (Lindestam Arlehamn et al., 2020). However, it is outside the scope of this report to consider all diseases that involve autoimmune processes, and the report focuses on diseases that have traditionally been termed autoimmune diseases, such as multiple sclerosis and SLE.

Similarly there is no consensus regarding the number of autoimmune diseases. The National Institute of Allergy and Infectious Diseases (NIAID) website states there are more than 80 diseases (NIAID, 2017), and the

Autoimmune Registry<sup>3</sup> and the Autoimmune Association<sup>4</sup> each list around 150 diseases (Autoimmune Association, 2021; Autoimmune Registry Inc., 2020). The National Institutes of Health's (NIH's) 2016–2018 triennial fiscal report to Congress discusses research applicable to autoimmune diseases in general as well as research on specific diseases, including SLE, multiple sclerosis, type 1 diabetes, myasthenia gravis, scleroderma, rheumatoid arthritis, myositis, juvenile idiopathic arthritis,<sup>5</sup> alopecia areata, psoriasis, pemphigus vulgaris, BACH2-related immunodeficiency and autoimmunity (BRIDA), and inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis (NIH, 2016, 2019). The report notes that SLE, multiple sclerosis, type 1 diabetes, IBD, and rheumatoid arthritis are among the most common and well-known autoimmune diseases and that BRIDA is a newly described autoimmune disease.

In the medical and research community, there are two differing approaches to characterize disease. One is to characterize and name diseases according to clinical criteria such as the presence of autoantibodies for autoimmune diseases (Hargraves et al., 1948; Marshall et al., 2018). Today, medical science classifies many rheumatologic, neurologic, gastrointestinal, cutaneous, hematologic, and cardiopulmonary illnesses as "autoimmune" based on the presence of autoantibodies, for example. The emphasis on clinical presentations of disease has resulted in disease classification by clinical diagnosis and organ system. A second approach to understanding diseases is to characterize them by their biologic mechanisms—the pathways that cause, mitigate, or affect the trajectory of disease. Over the past half century, the science of autoimmunity expanded beyond the concept of autoantibodies and autoreactive T cells and led to the emergence of the understanding of the importance of the innate immune response against self and other components of inflammation as drivers of autoimmune disease (Langan et al., 2020). Studies of innate immune cells, cytokines, cell surface markers, complement, and other biological phenomena now expand the definition of "autoimmune" to include illnesses with shared immunological mechanisms (Anaya, 2012; Cho and Feldman, 2015; Gokuladhas et al., 2021). Researchers can use an

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<sup>3</sup> The Autoimmune Registry, Inc., is a nonprofit organization that serves as a hub for research, statistics, and patient data on all autoimmune disease (Autoimmune Registry Inc., 2021).

<sup>4</sup> The Autoimmune Association (previously known as the American Association of Autoimmune Related Disorders [AARDA]) is a nonprofit organization focused on the eradication of autoimmune diseases and impact of autoimmunity (AARDA, 2017).

<sup>5</sup> Juvenile idiopathic arthritis comprises several types of arthritis: psoriatic arthritis, oligoarthritis, polyarthritis, enthesitis-related arthritis (spondyloarthropathy), and systemic arthritis (Still's disease). Source: <https://my.clevelandclinic.org/health/diseases/10370-juvenile-idiopathic-arthritis> (accessed February 1, 2022).

understanding of biologic mechanisms to target interventions for prevention, treatment, and cure.

There is no consensus regarding boundaries of the definition of autoimmune and autoinflammatory diseases. Public stakeholders, including people living with autoimmune disease, usually do not consider autoimmune and autoinflammatory conditions together, while clinicians and investigators may consider them similar and common enough to think of them as one entity or as two closely related entities. Regardless, the criteria for diagnosing someone as having an autoimmune disease may include diagnostic or classification criteria that describe clinically identifiable phenotypes in quantitative, exclusionary, time-limited, and binary terms (American Board of Medical Specialties, n.d.; Jia et al., 2017; Lockshin et al., 2021; Thompson et al., 2018). Nonetheless, diagnostic uncertainty is common among patients with autoimmune diseases.

### **Use of Autoimmune Disease Definitions in Research**

Both the clinical criteria and biologic mechanism approaches to disease classification play a role in research efforts to better understand autoimmune disease. Sociological and clinical research studies, including those that NIH supports, define autoimmune diseases narrowly, requiring consensus diagnostic and classification criteria. Criteria-defined diagnoses are prioritized in medical-specialty training and practice (Aggarwal et al., 2015b; American Board of Medical Specialties, n.d.) as well as in discourse by patient advocacy groups. However, criteria-based definitions of autoimmune illnesses exclude individuals who are atypical or who do not fulfill or are excluded by criteria definitions (Aggarwal et al., 2015b; Jia et al., 2017).

Biological purposes for using a diagnosis name are to support studies of mechanisms and /or phenotypes to develop interventions for individuals and to improve patient care. For these purposes, diagnosis names do not necessarily require that an individual fulfill a list of criteria. Indeed, mechanistic studies often include—and even focus on—atypical individuals whose slow illness evolution (“pre-disease”), clinical heterogeneity, and overlapping features exclude criteria-based diagnoses (Jia et al., 2017; Lockshin et al., 2015, 2019). However, clinical research protocols typically exclude individuals with autoimmune syndromes that do not meet formal classification or diagnostic criteria. These individuals are also difficult to identify in health statistics and medical billing databases. In addition, insurers may refuse to pay for tests and treatments for patients who do not fulfill criteria (Lockshin et al., 2021; Noah, 2022; Pinson, 2012).

**Finding:** Recent scientific advances regarding cellular and molecular mechanisms of tissue injury blur the line between autoimmune and autoinflammatory diseases, making differentiation between the two difficult.

**Finding:** There is no consensus on the number of autoimmune diseases.

**Finding:** Physicians and clinical researchers classify autoimmune diseases according to symptoms and laboratory abnormalities; basic science researchers classify autoimmune diseases according to more inclusive biological mechanisms. Lack of a consensus vocabulary impedes optimal research design and patient care.

**Conclusion:** *To improve research, guide patient care, and coordinate communication, clinical and research communities should develop a consensus vocabulary that includes both clinically defined autoimmune diseases and autoimmune mechanisms.*

### Causes of Autoimmune Diseases

Autoimmune diseases may have a known genetic or environmental cause or varying degree of both. When its etiology is unknown, an illness with an identifiable clinical or biologic phenotype is considered “idiopathic.” When an illness has a known exogenous cause, such as a bacterium or toxin, the disease is classified as having been induced by the exogenous agent (Bastard et al., 2020; Woodruff et al., 2021). Examples of exogenously induced autoimmune disease include procainamide-induced lupus (Blomgren et al., 1972), gadolinium-induced scleroderma (Idée et al., 2014), and various autoimmune phenomena, especially lung and gastrointestinal disease induced by chimeric antigen receptor (CAR) T-cell CD19/CD3 (Sedykh et al., 2018), anti-CD28 monoclonal antibody (Suntharalingam et al., 2006), and checkpoint-inhibitor (Johnson et al., 2018) treatments for malignancies. As highlighted by the COVID-19 pandemic, infections can play a role in inducing or exacerbating SLE (Quaglia et al., 2021) and cause other autoimmune diseases such as myocarditis (Boehmer et al., 2021). Environmental toxicants can also cause autoimmune disease illnesses such as Spanish toxic oil syndrome (Gelpí et al., 2002), eosinophilic fasciitis triggered by L-tryptophan ingestion (Beko et al., 1993), post-9/11 sarcoidosis-like syndrome (Webber et al., 2017), and myositis-like and scleroderma syndromes found in gold miners and workers in the polyvinyl chloride industry (Haynes and Gershwin, 1982; Tager and Tikly, 1999).

## Sex Differences in Autoimmune Diseases

Most autoimmune diseases are more prevalent in women than men, with conservative estimates attributing greater than 75 percent of autoimmune disease incidence to women (Desai and Brinton, 2019; Jacobson et al., 1997; Rubtsov et al., 2010). Among the exceptions are type 1 diabetes mellitus (Cartee et al., 2016) and myocarditis (Coronado et al., 2019; Fairweather et al., 2013), which occur more often in boys or men. Research suggests that sex and steroid hormones may contribute to these sex-related disparities. Sex hormones, both natural and synthetic, directly interact with cells of the immune system through receptors located on or inside immune cells (Bouman et al., 2005; Buskiewicz et al., 2016; Edwards et al., 2020). Steroid hormones, including estrogens and androgen, affect antibody production and immune cell proliferation and in this way can increase or inhibit immune response (Buskiewicz et al., 2016; Fairweather, 2014). In women, for example, estrogen is known to cause B cells to produce a greater antibody and autoantibody response compared with men (Potluri et al., 2019), while men can develop more severe inflammation in response to estrogen (Maggio et al., 2009; Tengstrand et al., 2003). Sources of hormones include external sources such as diet (e.g., soy), drugs (e.g., birth control pills), and skin care products, as well as the body, which produces steroids (Fairweather, 2014; Martin-Pozo et al., 2021; Patisaul, 2017). There is great research interest in understanding how sex hormones regulate the immune response.

Endocrine-disrupting chemicals such as phenols, parabens, and phthalates may influence sex differences in autoimmune diseases by altering sex hormone levels and/or ratios (Bruno et al., 2019; Castro-Correia et al., 2018; Edwards et al., 2018; Popescu et al., 2021). In addition, the X chromosome encodes many immune system genes, and dysregulated X-inactivation may contribute to sex differences in autoimmune diseases (Yuen, 2020). Much of our understanding of sex differences and the immune response during autoimmune disease is based on studies using animal models. In terms of prevalence and severity of disease, many animal models demonstrate a sex bias that is similar to that seen in human autoimmune diseases (Coronado et al., 2019; Nusbaum et al., 2020; Russman et al., 2018).

There is a semantic issue associated with sex and gender that is relevant to this research. The term sex generally refers to biological sex differences between males and females—chromosomes, hormones, and reproductive organs, for example—that affect health (Springer et al., 2012), while gender refers to the differences in socially constructed roles, characteristics, and behaviors of women and men (Springer et al., 2012; WHO, 2021). Separating the two constructs can be difficult, but labeling differences that occur in human research as “gender differences” rather than sex differences is not accurate either (Morgan et al., 2021). Given the

committee's focus on the effect of sex hormones and sex chromosomes on inflammation in relation to autoimmune disease pathogenesis, the committee chose to assume that most of the studies cited in this report involve biological sex differences. However, most of the source data did not distinguish between sex and gender differences when collecting or analyzing the data. The lack of clinical and animal studies that carefully define sex and gender in study design and that disaggregate data and conduct their analysis accordingly, rather than only controlling for sex, is a major gap in the field that future research might address. In fact, the research community has advocated for disaggregating data and analyses by sex and gender (Gebhard et al., 2020; Morgan et al., 2021).

**Finding:** Regarding research design, there is clinical research in which sex and gender have not been defined carefully and animal research in which sex has not been defined, thus preventing the disaggregation and analysis of data on autoimmune disease from being conducted accurately.

### Changing Definitions of Autoimmune Disease

Biological mechanisms are defining characteristics of autoimmune disease as they reflect poorly regulated function of one or many parts of inflammation pathways, such as antibodies/autoantibodies; macrophages, eosinophils, and T and B cells; cytokines; genes and gene expression; microbiome; detoxification pathways; and altered endothelium, mucosa, blood–brain, and placenta barrier tissue functions. For idiopathic, exogenously induced, and genetic forms of autoimmune diseases, the faulty mechanisms may operate independently, simultaneously, or in concert.

Although this report focuses on specific “idiopathic” autoimmune disease diagnoses, changing definitional boundaries of the diagnoses, different purposes of using diagnosis names, new data defining mechanisms in exogenously induced or genetic diseases, and new ways of thinking about disease mechanisms guarantee that, in the near future, there will be a need to restructure the concept of autoimmune disease. Scientific advances in genetics and epigenetics, for example, have helped to better distinguish illnesses with phenotypic characteristics or features seen in autoimmune diseases, such as Aicardi-Goutières syndrome and vacuoles-E1 enzyme-X-linked-autoinflammatory (VEXAS) syndrome (Beck et al., 2020; Crow and Rehwinkel, 2009) from autoimmune disease.

In summary, issues that make the committee's work difficult in responding to its charge are inherent in the concept of autoimmune disease: there are no standard definitions of either autoimmunity or autoimmune disease, the diseases are heterogeneous, and they last extended

periods of time. Moreover, some stakeholders conceptualize autoimmune diseases according to clinical criteria, while other stakeholders consider them to be biological entities with overlapping borders.

## OCCURRENCE AND COURSE OF AUTOIMMUNE DISEASES

### Data Sources and Limitations

Two commonly used measures to calculate the occurrence of a disease are incidence and prevalence. Incidence refers to the frequency of new occurrence in a population in a specified period of time—for example, the number of people newly diagnosed with a disease per year expressed as annual new cases per 100,000 persons (Porta, 2014). Prevalence refers to the total number of people with a disease in a defined time period, and it can include people recently diagnosed as well.

Incidence and prevalence data for autoimmune diseases in the United States are limited and can be difficult to find. There is no mandatory reporting system or national registry for autoimmune diseases. Much of the available incidence and prevalence data come from countries other than the United States with health care systems covering the entire population (Eriksson et al., 2013; Munk Nielsen et al., 2019; Pasvol et al., 2020; Wei et al., 2018).

For the purpose of this report, the committee sought high-quality epidemiology data, using criteria encompassing the size and diversity of the population studied and the ability to examine potential differences in disease rates across segments of the population, the length and recency of the time period covered, and the inclusion of a validation procedure to assess the accuracy of the classification criteria used to identify specific diseases within the database being used in the study. The committee preferred studies from the past decade (i.e., studies for which the data collection period included years since 2010), but such studies were unavailable for most of the autoimmune diseases selected for this report. The committee did not consider general population studies using self-reported data that did not include a medical record review for estimates of incidence or prevalence of autoimmune diseases because the accuracy of these methods is either unknown or poor (Videm et al., 2017).

Although the committee found data sources meeting some of these criteria for all of the selected diseases, none met all of the criteria. The most robust data come from studies of SLE, type 1 diabetes, and multiple sclerosis, described below:

- Data for primary Sjögren's disease were available from Manhattan, New York, through the Manhattan Lupus Surveillance

Program (2007 to 2009) (Izmirly et al., 2019). Because this effort was for a limited time period, this study does not provide data that allow assessing temporal trends in the incidence or prevalence of Sjögren's disease. These data focus only on Sjögren's disease (referred to as primary Sjögren's disease) and do not include individuals with Sjögren's disease along with other systemic rheumatic diseases such as rheumatoid arthritis and SLE. Sjögren's disease is diagnosed in up to 30 percent of individuals with rheumatoid arthritis and up to 20 percent of individuals with SLE (Aggarwal et al., 2015a; Baer et al., 2010; Harrold et al., 2020). These rates of Sjögren's disease co-occurrence, together with the prevalence of rheumatoid arthritis and SLE in Table 2-1, suggest that Sjögren's disease may occur more than 20 times more frequently when co-occurring with other autoimmune diseases than when diagnosed alone. Thus, the prevalence rate data limited to primary Sjögren's disease exclude the majority of individuals with Sjögren's disease.

- For SLE, incidence and prevalence data from the early 2000s (2002 to 2004 or 2007 to 2009) are available from a network of population-based national lupus registries in Michigan (Somers et al., 2014); Georgia (Lim et al., 2014); California (Dall'Era et al., 2017); Manhattan, New York (Izmirly et al., 2017); and American Indian or Alaskan Native populations (Izmirly et al., 2021a,b). Because this effort occurred for a limited time period, it does not provide data allowing for assessing temporal trends in the incidence or prevalence of SLE. The Centers for Disease Control and Prevention (CDC) supported these studies.
- For antiphospholipid syndrome (APS), incidence data from 2001 to 2015 are available from the Rochester Epidemiology Project (Duarte-Garcia et al., 2019); these data were used to estimate prevalence in 2015. The population base for this study is relatively small and homogenous. Because of the high proportion of people with SLE who also have APS, the relative lack of representation of groups who are at higher risk for SLE in this study population would result in an underestimation of APS rates.
- For rheumatoid arthritis (Kawatkar et al., 2019), incidence and prevalence data from 2005 to 2014 are available from the Kaiser Permanente medical system of Southern California, which covers a large and diverse population with respect to sociodemographic characteristics.
- For psoriasis, prevalence data from 1996 to 2009 from the Kaiser Permanente medical system of Northern California was used (Asgari et al., 2013).

- For IBD, prevalence data are available for 1999 to 2001 from a study using a large database from nine health maintenance organizations (Herrinton et al., 2007). For more recent prevalence data, studies include a 2007 to 2016 study that used two private administrative health claims databases collectively covering approximately 62 million people annually (Ye et al., 2020), as well as studies in more limited populations (Hou et al., 2013; Shivashankar et al., 2017; Xu et al., 2021). The committee relied on the estimates of the larger study, while considering the variability in estimates and the strengths and limitations of this set of studies (see Box 2-1).
- For celiac disease, serology (tissue transglutaminase and endomysial IgA antibodies) data from the 2009 to 2012 National Health and Nutrition Examination Survey<sup>6</sup> are available (Mardini et al., 2015). Although this study provides data on the prevalence of these antibodies in a representative sample of the U.S. population, it does not include symptom data or other details allowing for assessing disease status based on a full clinical evaluation.
- For primary biliary cholangitis (PBC), prevalence data from 2003 to 2014 are available from the Fibrotic Liver Disease Consortium (Lu et al., 2018), a large network of health care systems drawing patients from across the United States.
- For multiple sclerosis, prevalence data from 2008 to 2010 are available from a study using three public (Veterans Administration, Medicare, and Medicaid) and three private administrative health claims databases collectively covering 125 million U.S. adults (Culpepper et al., 2019; Nelson et al., 2019; Wallin et al., 2019). The data were weighted to reflect the source of insurance coverage in the U.S. population, and the study used a validation procedure to assess the sensitivity and specificity of the classification criteria. However, the design of this study did not allow for assessing incidence rates or differences in prevalence among racial or ethnic groups, or assessment of temporal trends in incidence or prevalence. The National Multiple Sclerosis Society initiated and supported this study.
- For type 1 diabetes, incidence data from 2002 to 2012 and prevalence data from 2001 to 2009 are available from the SEARCH for Diabetes in Youth study, a large population-based study conducted at five centers across the United States (Dabelea et al.,

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<sup>6</sup>CDC conducts the National Health and Nutrition Examination Survey, which uses health interview, physical examination, and biospecimen data to assess the health and nutritional status of U.S. adults and children (NHANES, 2017).

2014; Mayer-Davis et al., 2017). CDC and the National Institute of Diabetes and Digestive and Kidney Diseases initiated and supported this study.

- The committee did not find any recent (year 2000 or later) studies of incidence or prevalence of autoimmune thyroid diseases in the United States.

In contrast, the Surveillance, Epidemiology, and End Results (SEER) database (NCI, 2021b) developed by the National Cancer Institute, provides easily accessible, verified data on incidence, prevalence, and mortality rates for the U.S. population in total, for males, females, as well as for five race and ethnicity groups, for all cancers, and for more than 30 individual types of cancers. It also provides trends in these rates over the past 20 years. This kind of resource is not available for autoimmune diseases.

The committee did take special note of the usefulness of the Olmsted County, Minnesota, Rochester Epidemiology Project (St. Sauver et al., 2011) conducted by the Mayo Clinic. This resource has provided epidemiologic data for rheumatoid arthritis, SLE, IBD, and many other autoimmune (and other) diseases since the 1960s, and is one of the few sources of long-term data on trends in the occurrence of these diseases. It is also a resource used for studies of prognosis, concomitant illnesses, and autoimmune-related mechanisms in other diseases. An important limitation, however, is that it covers a relatively small and homogenous population in terms of sociodemographic background,<sup>7</sup> and the sample size is small for many of these diseases. NIH continues to support the Rochester Epidemiology Project.

**Finding:** There is no mandatory reporting system or national population-based data-collection program for autoimmune diseases, as there is for cancer through the National Cancer Institute's SEER system.

There are also difficulties with respect to obtaining accurate data on mortality relating to autoimmune diseases. Death certificates can provide population-level data on mortality from autoimmune diseases, but they are not a good source of data pertaining to occurrence of chronic conditions that are not associated with acute mortality risks, such as most autoimmune diseases. Death certificates include information on immediate and underlying causes of death, with an additional field for other significant conditions contributing to the death. However, the completeness

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<sup>7</sup> U.S. census data for Olmsted County, Minnesota, in 2000 reported a population size of 124,277 with 90.3 percent of residents identifying as White and 6.4 of residents reporting incomes below the poverty level (Rochester Epidemiology Project, 2012).

**BOX 2-1**  
**Variation in Inflammatory Bowel Disease Estimates**

The difficulty in finding basic, up-to-date, accurate data on the occurrence of autoimmune diseases can be illustrated by the IBD ulcerative colitis, and Crohn's disease. Extensive search for data on the U.S. prevalence of these diseases yielded six studies with varying strengths that produce estimates for the prevalence in 2020 that range from 1.2 to almost 4.0 million.

As with many other autoimmune diseases, these estimates do not include undiagnosed disease in people with mild symptoms.

1. One study provides estimates for IBD, ulcerative colitis, and Crohn's disease from 2007 to 2016 based on two health insurance claims databases encompassing approximately 62 million lives annually (Ye et al., 2020). Extrapolating to the 2020 U.S. population yields an estimated 1.2 million people with ulcerative colitis, Crohn's disease, or unspecified IBD. The claims data come from private insurance companies, limiting the generalizability of the results. Investigators validated the algorithm within the Canadian health care system. The study does not provide a basis for examining differences in rates by racial, ethnic, or socioeconomic factors, but it does allow for the examination of changes in rates over this time period.
2. Another group derived its IBD prevalence estimates from 1999 to 2001 from a database of 1.8 million members of nine health maintenance organizations (Herrinton et al., 2007). This study included a validation protocol using medical records from the database. These are the oldest data among the studies the committee examined, however, and so would not account for any increases in prevalence over the past 20 years. The study also does not provide a basis for examining differences in rates by racial, ethnic, or socioeconomic factors. Extrapolating to the 2020 U.S. populations produces an estimated 1.3 million people with ulcerative colitis, Crohn's disease, or unspecified IBD.

and accuracy of this assessment, particularly for deaths relating to autoimmune diseases, is low: studies have demonstrated considerable under-reporting of autoimmune diseases as a cause of death, with no mention of an underlying condition in 40 to 80 percent of deaths of people enrolled in clinical cohort studies of SLE and rheumatoid arthritis (Calvo-Alén et al., 2005; Molina et al., 2015). It may be difficult to quantify mortality in most autoimmune diseases since death more commonly results from—and is recorded as being the result of—complications such as cardiovascular disease, infection, or malignancy rather than specific disease causes such as lethal hemorrhage resulting from thrombocytopenia. Studies of the age at death of persons with diagnosed autoimmune diseases constitute an indirect measure of mortality. A recent Dutch study that used death

3. Relatively recent (2011) estimates of incidence and prevalence of IBD are based on data from Olmsted County, Minnesota (Shivashankar et al., 2017). The authors noted the rates in this study were among the highest reported in the United States. Extrapolating to the 2020 U.S. population produces an estimated 1.7 million people with ulcerative colitis or Crohn's disease. This study likely overestimates disease prevalence when extrapolating to the entire U.S. population because the study population was predominantly White and rates of these diseases are considerably higher in White persons compared with other groups.
4. Extrapolating from a study in a national Veterans Affairs health service population conducted between 1998 and 2009 (Hou et al., 2013) to the 2020 U.S. population yields an estimate for the prevalence of IBD at 2.3 million. Although this is a national database, it is a selected population (i.e., veterans). The denominator for the rate calculations is the number of people who used health care services, rather than all people in the study population, which may result in an overestimate of the rate of disease.
5. One study provides estimates based on Medicare data for about 25 million beneficiaries in patients aged 67 and older not enrolled in a health maintenance organization (Xu et al., 2021). It is not possible to extrapolate estimates from this age group to the entire U.S. population.
6. A representative sample of the U.S. population based on the 2015 National Health Interview Survey provides prevalence estimates (Dahlhamer et al., 2016). Extrapolating to the 2020 U.S. population yields an estimated 3.9 million people. This study is based on self-report ("Have you ever been told by a doctor or other health professional that you had Crohn's disease or ulcerative colitis?") in a general population setting, with no verification from medical records and no information on the accuracy of responses. As noted previously, the committee did not consider studies using self-reported data, without medical record review.

certificate data concluded that "Systemic autoimmune diseases constitute a rare group of causes of death, but contribute to mortality through multiple comorbidities. Classification systems could be adapted to better encompass these diseases as a category" (Mitratza et al., 2021).

The committee also noted challenges in conducting and interpreting some clinic-based studies of mortality risk among people with specific autoimmune diseases. For example, studies based in tertiary care center(s) limit the generalizability of the findings. It is also important to distinguish between incidence and prevalence in analysis of risk over time, to report absolute risk in addition to relative risk, to address loss to follow-up, and to include a sample large enough to be able to examine the experiences of specific sociodemographic groups within the patient population.

**Finding:** There is a lack of accurate data on mortality associated with autoimmune diseases. Death certificates may provide incomplete information on an underlying autoimmune disease that contributed to the cause of death.

### *Additional Data Challenges*

Studies using International Classification of Diseases (ICD) 9 or ICD 10 codes in electronic medical records to identify potential cases of autoimmune diseases may be inadequate (Moores and Sathe, 2013). Other information, such as number of visits with specific codes, medication use, and results of specific types of laboratory tests can improve the accuracy of the case ascertainment methods (Barnado et al., 2017; Liao et al., 2010). Researchers can conduct a complete medical record review to evaluate a case ascertainment algorithm's sensitivity and specificity within the database being used (Carroll et al., 2012). Insurance-based algorithms used in the United States present an additional difficulty in terms of determining initial diagnosis for incidence studies, as medical records may be incomplete because of changes in coverage or providers. The pattern of remissions and flares seen in some autoimmune diseases presents additional challenges to determining disease prevalence. Prevalence studies based on current medication use or a specified frequency of medical visits may undercount patients experiencing prolonged periods of remission.

### **Estimates of Overall Prevalence of Autoimmune Diseases**

In 1997, a compilation and analysis of studies reporting incidence or prevalence data for diseases estimated that at least one autoimmune disease would occur in approximately 8.5 million U.S. residents, or 3.2 percent of the population (Jacobson et al., 1997). This was the first attempt to estimate the overall burden of autoimmune diseases as a class of diseases, and it used a literature-survey approach, collecting studies published since 1965. A subsequent analysis building on this work expanded the number of autoimmune diseases to 31, used country-specific (Denmark) hospitalization data to better estimate more current disease patterns, and accounted for co-occurrence of diseases, resulting in an estimate of overall prevalence of greater than 5 percent (Eaton et al., 2007). This analysis may underestimate diseases that generally do not require hospitalizations or clinic visits in a specific time period. For example, prevalence rates for alopecia, psoriasis, and hypothyroidism were three to five times lower in this study compared with other studies from European populations. Accounting for this deficiency resulted in an overall estimate of 7.6 to 9.4 percent for a set of 29 autoimmune diseases (Cooper et al., 2009).

These estimates are all based on the prevalence of autoimmune diseases, rather than the prevalence of people with autoimmune diseases. Because many people have more than one autoimmune disease, the number of people with any autoimmune disease is less than the number suggested by summing the prevalence of individual autoimmune diseases. The sum of the prevalence of individual diseases will be larger than the sum of individuals with any autoimmune disease, with the difference reflecting the degree of over-counting resulting from multiple diseases occurring within an individual. A study in seven provinces in Canada estimated the combined prevalence of systemic autoimmune rheumatic disease (SLE, scleroderma, primary Sjögren's disease, and polymyositis/dermatomyositis) and counted individuals with one or more of these diseases. The estimated prevalence of this group of diseases was 200 to 500 per 100,000 (Brotén et al., 2014). This is likely a low estimate for the systemic rheumatic diseases, given the low sensitivity of the disease classification algorithms used and the exclusion of rheumatoid arthritis from this analysis.

Another way to estimate total burden of a group of diseases is by cumulative incidence or lifetime risk. For example, the estimate of the lifetime risk of all cancers combined, based on 2016 to 2018 SEER data was 39.2 percent (NCI, 2021a), with individual risks for colon, lung, and breast cancer each being greater than 4 percent. In an analysis of lifetime risk of systemic rheumatic diseases (rheumatoid arthritis, SLE, psoriatic arthritis, polymyalgia rheumatica, giant cell arteritis, ankylosing spondylitis, primary Sjögren's disease) in Olmsted County, Minnesota, the lifetime risk was 8.42 percent in women and 5.13 percent in men (Crowson et al., 2011). Notably, this analysis does not include multiple sclerosis, thyroid diseases, type 1 diabetes, or other autoimmune diseases, which would most likely increase these estimates several fold.

## Epidemiology of Select Autoimmune Diseases

### *Prevalence Rates*

Among the most common autoimmune diseases are celiac disease, rheumatoid arthritis, and psoriasis, with prevalence rates approximately 790 to 939 per 100,000 and approximately 2.3 to 2.5 million U.S. residents living with each of these diseases; IBD, with a prevalence rate of approximately 500 per 100,000; multiple sclerosis, with a prevalence rate of approximately 300 per 100,000; and type 1 diabetes, with a prevalence rate of approximately 190 per 100,000 (Table 2-1). The available data pertaining to Sjögren's disease are limited to primary Sjögren's disease,

which does not occur in conjunction with SLE, rheumatoid arthritis, or scleroderma, and so underestimates the overall burden of this condition.

Table 2-1 does not include the autoimmune thyroid diseases Graves' disease (hyperthyroidism) and Hashimoto's thyroiditis (hypothyroidism) because of a lack of U.S. data covering the past 20 years. A study of Graves' disease from 2008 to 2013 in Sheffield, United Kingdom, reported an annual incidence of 24.8 cases per 100,000 persons, with a median age at diagnosis of 44 (33 to 56) years; 80 percent of patients were women (Hussain et al., 2017). A large cohort study from the Netherlands examined thyroid medication use and thyroid hormone levels to classify overt and subclinical thyroid diseases; 3.1 percent of participants reported levo-thyroxine use, and 9.4 percent of the people who were not taking thyroid medications had subclinical hypothyroidism (thyroid stimulating hormone levels of 4.01–10.0 milli-International Units per liter) (Wouters et al., 2020).

#### *Trends in Incidence and Prevalence*

Trends in disease incidence are important indicators of changes in the underlying risk factors for the disease, such as an increasing or decreasing level of an environmental exposure that contributes to the development of the disease. These rates can best be ascertained from studies applying the same case ascertainment methods over time within a specific population. Trend data from U.S. studies spanning periods within the past 20 years and meeting these criteria were not available for psoriasis, multiple sclerosis, or the autoimmune thyroid diseases; for psoriasis and multiple sclerosis, the committee has included data from Canada in the following summary.

Only one study, of psoriasis incidence in Ontario, Canada, reported decreasing incidence for time periods covering 2000 to 2015 (Table 2-2). Studies of Sjögren's disease, rheumatoid arthritis, PBC, and in some studies of IBD (ulcerative colitis and Crohn's disease) and type 1 diabetes, found increasing incidence rates compared with pre-2000 years or during the 2000s. There was little or no trend observed in the studies of APS and multiple sclerosis.

Trends in disease prevalence can reflect changes in the incidence of disease, in the age distribution of a population, or in survival of people with the disease. Multiple sclerosis (Rotstein et al., 2018) and PBC (Lu et al., 2018) are examples of diseases for which studies have demonstrated that prevalence increased despite little change in incidence; reductions in mortality rates were also observed among people with these diseases.

In children and adolescents, the incidence or prevalence of two of the most common autoimmune diseases, IBD and type 1 diabetes, appears to have increased in the United States since 2000 (Table 2-2). The pediatric

**TABLE 2-1** Prevalence Rates of Selected Autoimmune Diseases, United States

Disease	Study Design and Data Source	Area, Time Period	Age	Prevalence Rate (per 100,000)			Estimated U.S. Total in 2020 <sup>a</sup>
				Total	Females	Males	
Sjögren's disease (primary) <sup>b</sup>	Population-based study using Manhattan Lupus Surveillance Program Registry	Manhattan, NY 2007	≥ 18	13.1	21.1	3.5	35,370
Systemic lupus erythematosus	Population-based study using data from 4 CDC SLE registries and Indian Health Service	GA, MI: 2002–2004 CA, Manhattan, NY, and Indian Health Service: 2007–2009	All ages	72.8	128.7	14.6	206,000
Antiphospholipid syndrome	Population-based study, Rochester Epidemiology Project	MN 2001–2015	≥ 18	50	51	48	123,000
Rheumatoid arthritis	Population-based, Kaiser Permanente, patient electronic records	Southern, CA 2014	≥ 18	890.0	1326.0	387.0	2,403,000

*continued*

**TABLE 2-1** Continued

Disease	Study Design and Data Source	Area, Time Period	Age	Prevalence Rate (per 100,000)			Estimated U.S. Total in 2020 <sup>a</sup>
				Total	Females	Males	
Psoriasis	Population-based study, Kaiser Permanente, patient electronic, computerized records	Northern CA, 2009	≥ 18	939.0	No sex difference reported	No sex difference reported	2,535,000
	Population-based study, Truven Health, patient electronic, computerized records	U.S. 2015	< 18	128.0	146.0	110.0	94,768
Inflammatory bowel disease <sup>c</sup>							
Ulcerative colitis	Retrospective cross-sectional study using two health claims databases	U.S. 2016	≥ 18	181.1	NA	NA	464,000
			2-17	21.6			16,400
Crohn's disease	Retrospective cross-sectional study using two health claims databases	U.S. 2016	≥ 18	197.7	NA	NA	504,000
			2-17	45.9			35,000
Total IBD <sup>d</sup>	Retrospective cross-sectional study using two health claims databases	U.S. 2016	≥ 18	478.4	NA <sup>e</sup>	NA <sup>f</sup>	1,217,000
			2-17	77.0			58,000

Celiac disease (based on serology)	Population-based, representative U.S. population sample, NHANES	U.S. 2009–2012	> 5	790.0	NA	NA	2,346,000
Primary biliary cholangitis	Fibrotic Liver Disease Consortium data from 11 health systems	U.S. 2014	All ages	39.2	57.8	15.4	129,000
	Retrospective, cross-sectional population-based study using three public and three private administrative health claims databases	U.S. 2008–2010	≥ 18	309.2 <sup>a</sup>	450.1	159.7	775,000
Type 1 diabetes	Population-based study, SEARCH data from five participating centers in CA, CO, OH, SC, WA and select American Indian reservations	U.S. 2009	< 20	193.0	193.0	193.0	178,000

<sup>a</sup> U.S. total population estimates for Sjögren's disease, rheumatoid arthritis, psoriasis, and primary biliary cholangitis were calculated by applying total prevalence rate to 2020 U.S. census population estimates (330 million all ages; 270 million age ≥ 18; 297 million > age 5; 92.4 million < age 20). The SLE estimate was calculated by extrapolating the estimate from (Izmirly et al., 2021b) based on 2018 U.S. census data to 2020 using the percentage increase in total population from 2018 to 2020. The APS estimate was calculated by extrapolating the 2015 estimate provided by (Duarte-Garcia et al., 2019) to 2020 U.S. census population estimates. Inflammatory bowel disease estimates were calculated by extrapolating the 2016 estimates provided by (Ye et al., 2020) to 2020 U.S. census population estimates. The multiple sclerosis estimate was calculated by extrapolating the 2010 estimate provided by (Wallin et al., 2019) to 2020 U.S. census population estimates.

**TABLE 2-1** Continued

<sup>b</sup> Sjögren's disease commonly co-occurs with other systemic rheumatic diseases (including up to 30% of individuals with rheumatoid arthritis and up to 20% of individuals with SLE (Aggarwal et al., 2015a; Baer et al., 2010; Harrold et al., 2020)), but this was not included in the studies of primary Sjögren's disease. If these individuals are included, prevalence of all Sjögren's disease would be estimated to be on the order of 800,000 in the United States in 2020. However, this figure does not account for individuals with Sjögren's disease and other systemic autoimmune diseases (e.g., dermatomyositis, systemic sclerosis) or for children.

<sup>c</sup> See Box 2-1 for further discussion of variability in inflammatory bowel disease estimates.

<sup>d</sup> Includes ulcerative colitis, Crohn's disease, and unspecified inflammatory bowel disease.

<sup>e</sup> Reported 54.5 percent of adults in pooled databases were female.

<sup>f</sup> Reported 55.0 percent of pediatric patients in pooled databases were male.

<sup>g</sup> Estimates reported are adjusted 10-year cumulative prevalence per 100,000.

NOTES: CA, California; CDC, Centers for Disease Control and Prevention; GA, Georgia; CO, Colorado; IBD, inflammatory bowel disease; MI, Michigan; MN, Minnesota; NHANES, National Health and Nutrition Examination Survey; NY, New York; OH, Ohio; SC, South Carolina; SEARCH, SEARCH for Diabetes in Youth study; SLE, systemic lupus erythematosus; U.S., United States; WA, Washington.

SOURCES: Sjögren's disease (primary) (Izmirly et al., 2019); systemic lupus erythematosus (Izmirly et al., 2021b); antiphospholipid syndrome (Duarte-Garcia et al., 2019); rheumatoid arthritis (Kawatkar et al., 2019); psoriasis ≥ 18 (Asgari et al., 2013), < 18 (Paller et al., 2018); inflammatory bowel disease: ulcerative colitis, Crohn's disease, and total IBD (Ye et al., 2020); celiac disease (Mardini et al., 2015); primary biliary cholangitis (Lu et al., 2018); multiple sclerosis (Wallin et al., 2019); type 1 diabetes, (Dabelea et al., 2014).

**TABLE 2-2** Trends in Incidence or Prevalence of Autoimmune Diseases in the United States and Canada

Disease	Study Design and Data Source	Area, Time Period	Age	Incidence	Prevalence
Sjögren's disease (primary)	Population-based study using Rochester Epidemiology Project data	Olmstead County, MN 1976–2015	≥ 18	Fluctuating (wavelike) rates, with higher values around 1990, 2005, and 2015, with overall increasing trend ( $p=0.005$ )	—
Antiphospholipid syndrome	Population-based study using Rochester Epidemiology Project data	Olmstead County, MN 2001–2015	≥ 18	No trends observed	—
Rheumatoid arthritis	Population-based study using Rochester Epidemiology Project data	Olmstead County, MN 1995–2007	≥ 18	Increased in women from 1995 to 2007 by about 2.5 percent per year	—
	Population-based study using Kaiser Permanente, patient electronic records	Southern CA 1995–2014	≥ 18	Average annual increase from 1995 to 2014 was 3 percent (95 percent CI, -4 percent to 10 percent), relatively steady from 2005 to 2014	—

*continued*

**TABLE 2-2** Continued

Disease	Study Design and Data Source	Area, Time Period	Age	Incidence	Prevalence
Psoriasis	Population-based study using health administrative data	Ontario, Canada 2000–2015	≥ 20	Decreased from 111.0 to 69.0 per 100,000 per year	Increased from 1,740 to 2,320 per 100,000
Inflammatory bowel disease					
Ulcerative colitis	Population-based study using Rochester Epidemiology Project data	Olmstead County, MN 1970–2010	All ages	Increased from 9.2 to 12.2 per 100,000 per year (p=0.06)	Increased from 241.0 to 286.3 per 100,000
	Population-based study, Kaiser Permanente, patient electronic records	Northern CA 1996–2002	0–17	Increased from 1.8 to 4.9 per 100,000 per year (p<0.001)	—
Crohn's disease	Population-based study using Rochester Epidemiology Project data	Olmstead County, MN 1970–2010	All ages	Increased from 6.9 to 10.7 per 100,000 per year (p=0.003)	Increased 174.0 to 246.7 per 100,000
	Population-based study, Kaiser Permanente, patient electronic, computerized records	Northern CA 1996–2006	0–17	Increased from 2.2 to 4.3 per 100,000 per year (p=0.09)	—
All IBD*	Retrospective cross-sectional study using two health claims databases	U.S. 2007–2016	≥ 18	—	Increased from 214.9 to 478.4 per 100,000
			2–17	—	Increased from 33.0 to —

Primary biliary cholangitis	Population-based study 24 zip-code areas in Midwestern WI 1992–2011	$\geq 18$	The overall age- and sex-standardized annual incidence rate increased, though not significantly	—	
			Increased in females from 6.9 cases per 100,000 per year 1992–1996 to 11.3 cases per 100,000 per year 2002–2006; rates steady from 2002 to 2011		
Fibrotic Liver Disease Consortium data from 11 health systems	2006–2014	All ages	Increased from 4.2 per 100,000 per year (2006) to 4.3 per 100,000 per year (2014)	From 2006 to 2014, increased from 33.5 to 57.8 per 100,000 in women; from 7.2 to 15.4 per 100,000 in men; total rate change, from 21.7 to 39.2 per 100,000	
Multiple sclerosis	Population-based study using Province of Ontario administrative health data	Ontario, Canada 1996–2013	$\geq 20$	Generally stable except for short-term increase 2010–2013	Increased from 157 to 265 per 100,000

*continued*

**TABLE 2-2** Continued

Disease	Study Design and Data Source	Area, Time Period	Age	Incidence	Prevalence
Type 1 diabetes Incidence:	Population-based study, SEARCH data from five participating centers in CA, CO, OH, SC, WA, and select American Indian reservations	SEARCH 2002–2012	< 20	Increased from 19.5 per 100,000 per year in 2002–2003 to 21.7 per 100,000 per year in 2011–2012; annual increase, 1.4 percent; p=0.03)	—
	Population-based study, SEARCH data from five participating centers in CA, CO, OH, SC, WA, and select American Indian reservations	SEARCH 2001–2009	< 20	—	Increased from 148 to 193 per 100,000
	Population-based study using Rochester Epidemiology Project data	Olmstead, MN 1994–2010	All ages	Average annual incidence rate was 9.2 per 100,000 per year, little variation or trend	—
	Population-based study using MarketScan Multi-State Medicaid Claims Database	U.S. (Medicaid population) 2002–2016	< 18	—	Increased from 129 to 234 per 100,000

\* Includes ulcerative colitis, Crohn's disease, and undifferentiated IBD.

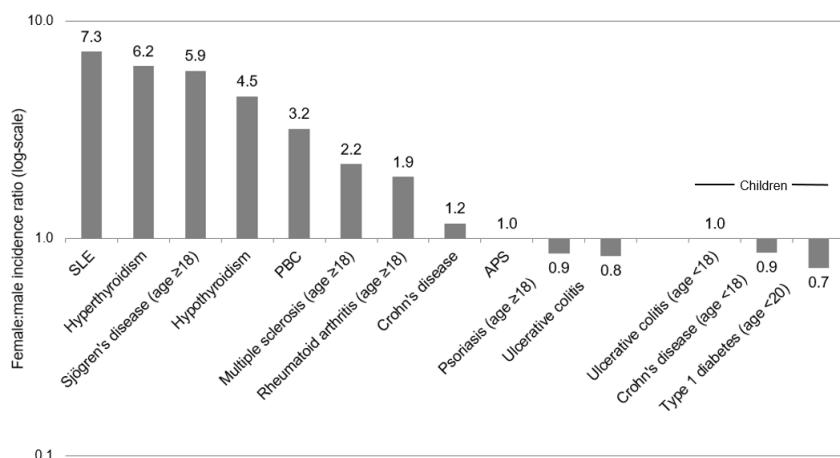
NOTE: CA, California; CI, confidence interval; CO, Colorado; IBD, inflammatory bowel syndrome; MN, Minnesota; OH, Ohio; SC, South Carolina; U.S., United States; WA, Washington; WI, Wisconsin.

SOURCES: Sjögren's disease (primary) incidence (Maciel et al., 2017a); antiphospholipid syndrome (Duarte-Garcia et al., 2019); rheumatoid arthritis (1) (Myasoedova et al., 2010), (2) (Kawatkar et al., 2019); psoriasis (Eder et al., 2019); IBD: ulcerative colitis all ages (Shivashankar et al., 2017), 0–17 (Abramson et al., 2010); Crohn's disease all ages (Shivashankar et al., 2017), 0–17 (Abramson et al., 2010); all IBD (Ye et al., 2020); primary biliary cholangitis  $\geq$  18 (Kanth et al., 2017), all ages (Lu et al., 2018); multiple sclerosis (Rotstein et al., 2018); type 1 diabetes: incidence  $<$  20 (Mayer-Davis et al., 2017), prevalence  $<$  20 (Dabelea et al., 2014), incidence all ages (Cartee et al., 2016), prevalence  $<$  18 (Chen et al., 2019).

prevalence of IBD in the United States increased between 2007 to 2016 from 33.0 to 77.0 per 100,000, with Crohn's disease being twice as prevalent as ulcerative colitis (45.9 versus 21.6) (Ye et al., 2020). Type 1 diabetes has also increased. From 2001 to 2009, a large U.S. study showed an increase in type 1 diabetes prevalence from 148 per 100,000 to 193 per 100,000 (Dabelea et al., 2014). A subsequent study of the U.S. Medicaid pediatric population during the period 2002 to 2016 showed an increase in annual type 1 diabetes prevalence from 129 to 234 per 100,000 (Chen et al., 2019). This trend was not seen, however, in a study spanning 1994 to 2010 in Olmsted County, Minnesota (Cartee et al., 2016).

### *Demographic Patterns with Respect to Disease Risks*

Many, but not all, autoimmune diseases affect women predominantly (Figure 2-1). The diseases with the most marked sex difference in occurrence, with female-to-male ratios greater than 5:1 are SLE (Izmirly et al.,



**FIGURE 2-1** Variation in female-to-male ratio in incidence rates across the autoimmune diseases of focus.

NOTES: Age ranges provided when available.

APS, antiphospholipid syndrome; PBC, primary biliary cholangitis; SLE, systemic lupus erythematosus.

SOURCES: Data drawn from the following studies that provided sex-specific incidence rates. SLE (Izmirly et al., 2021a); Sjögren's disease (Maciel et al., 2017a); hyperthyroidism (Leese et al., 2008); PBC (Lu et al., 2018); hypothyroidism (Leese et al., 2008); rheumatoid arthritis (Myasoedova et al., 2010); Crohn's disease (Herrinton et al., 2008); APS (Duarte-Garcia et al., 2019); psoriasis (Icen et al., 2009); ulcerative colitis (Herrinton et al., 2008); multiple sclerosis (Langer-Gould et al., 2013); ulcerative colitis, children (Abramson et al., 2010); Crohn's disease, children (Abramson et al., 2010); type 1 diabetes (Cartee et al., 2016).

2021a,b), hyper- and hypothyroidism (Leese et al., 2008), and Sjögren's disease (Maciel et al., 2017a, 2017b). The female-to-male ratio is lower, between 4:1 and 2:1, for multiple sclerosis (Langer-Gould et al., 2013), PBC (Lu et al., 2018), systemic sclerosis (Mayes et al., 2003), and rheumatoid arthritis (Myasoedova et al., 2010). However, for other autoimmune diseases, such as psoriasis (Icen et al., 2009), the female-to-male incidence ratio is close to or less than 1.0 and also influenced by age. Myocarditis, for example, occurs more frequently in males before age 50 (Coronado et al., 2019). Although the female-to-male ratio for APS is close to 1.0 in the only population-based study available (Duarte-Garcia et al., 2019), this ratio may be higher in populations that include a greater proportion of patients with SLE.

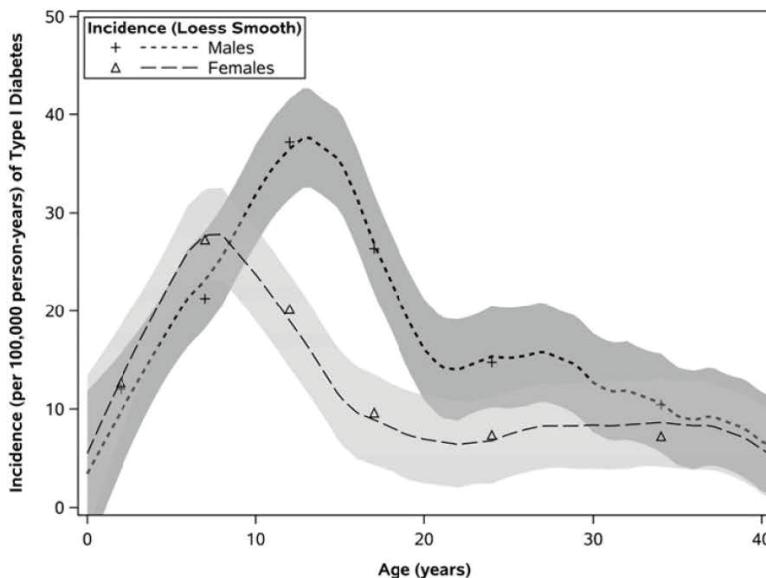
Regarding disease incidence in children, one study of juvenile idiopathic arthritis found an increased incidence in females compared with males in each of the age groups studied (ages 0 to 5, 6 to 10, and 11 to 15 years) (Harrold et al., 2013). Other autoimmune diseases do not show a female predominance in children, and some diseases, such as type 1 diabetes (Cartee et al., 2016), occur more frequently in boys than girls.

Although most autoimmune diseases can occur at any age, different diseases present different patterns with respect to age at onset or diagnosis. Figure 2-2 shows four patterns, all based on recent studies from Olmsted County, Minnesota. Type 1 diabetes most often occurred between 5 and 15 years of age, but incidence extended through ages 30 to 39, and rates were higher for males compared with females beginning around age 10. Incidence rates for primary Sjögren's disease increased steadily throughout adulthood, reaching the highest rates around ages 65 to 74, with higher incidence seen in women (Maciel et al., 2017a). The peak age at diagnosis of Crohn's disease and ulcerative colitis was 20 to 29 years, but the study also saw new cases through early and late adulthood. There was little difference in rates between males and females for Crohn's disease, but for ulcerative colitis, rates in males were somewhat higher than in females.

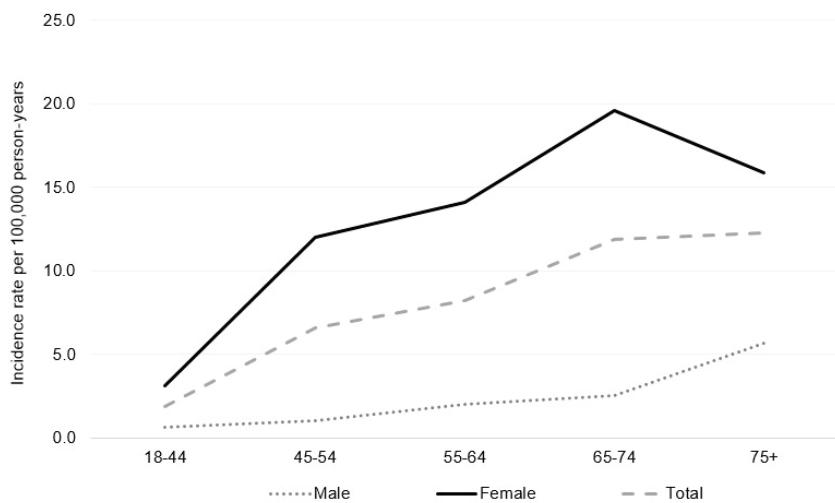
### *Health Disparities in Autoimmune Diseases*

There are known disparities in the incidence, prevalence, severity, prognosis, outcomes, and care related to autoimmune diseases. These disparities adversely affect groups that are socially disadvantaged and marginalized based on race and ethnicity, socioeconomic status, and geographic region. In addition, these factors may interact with one another to cause, accentuate, and perpetuate health disparities at the individual patient, community, and societal levels (Reifsnyder et al., 2005). While studies may report race and ethnicity as a biologic proxy for genetic origin, the committee acknowledges

## A. Type 1 Diabetes



## B. Primary Sjögren's Disease

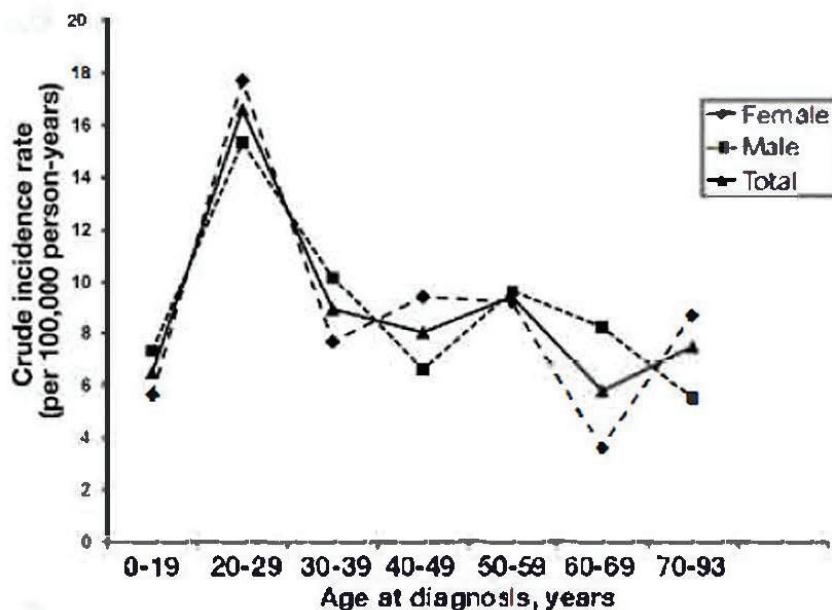


**FIGURE 2-2** Incidence rates of four autoimmune diseases by age and sex in Olmsted County, Minnesota. A. Type 1 diabetes, 1994–2010. B. Primary Sjögren's disease, 1976–2015. C. Crohn's disease, 1970–2010. D. Ulcerative colitis, 1970–2010.

NOTE: Per 100,000 person-years = annually per 100,000 persons.

SOURCES: A. Cartee et al., 2016; B. Figure created using data from Maciel et al., 2017a; C. and D. Shivashankar et al., 2017.

## C. Crohn's Disease



## D. Ulcerative Colitis

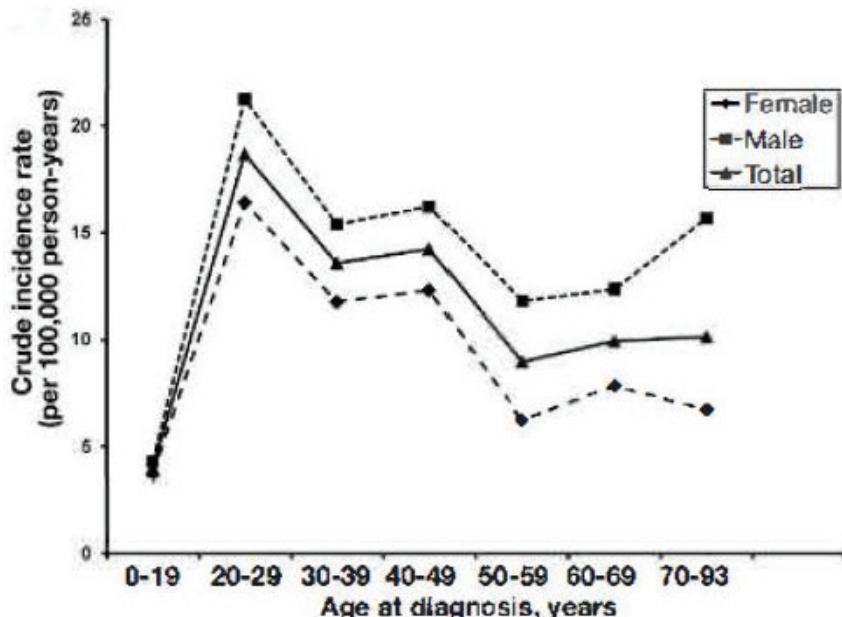


FIGURE 2-2 Continued

that the terms “race” and “ethnicity” denote the full breadth of experiences and exposures of a population, rather than a limited lens focused on genetic variability among populations (see Box 2-2).

With respect to racial and ethnic disparities in incidence or prevalence of disease, it is important to note that no single pattern describes the patterns seen among the autoimmune diseases; for some diseases, the highest rates occur among Black individuals, while for other diseases, the highest rates occur in White individuals (Figure 2-3). Studies have reported increased rates of juvenile idiopathic arthritis, autoimmune liver disease, and SLE in Indigenous peoples in the United States and Canada (Barnabe et al., 2012; Mauldin et al., 2004; Yoshida et al., 2006). These studies reinforce the need for more directed research into autoimmune disease risk in American Indian and Alaska Native populations.

Studies have also found disparities in the severity and prognosis of many diseases according to race and ethnicity (Barton et al., 2011; Lim et al., 2019; Ventura et al., 2017). Barriers to diagnosis, access to specialist care or to enrollment in clinical trials, and affordability of treatments are all issues that can affect people with autoimmune diseases (Bailey et al.,

### **BOX 2-2** **The Constructs of Race and Ethnicity**

Race and ethnicity have historically been characterized as biological variables. However, these categorizations represent social constructs that are not synonymous with genetics or ancestry. Studies have shown that genetic variation contributes to only a small portion of differences among racial and ethnic groups, and that self-reported race or ethnicity often do not align with ancestry demonstrated by genetic data (Mersha and Abebe, 2015; Sankar et al., 2004).

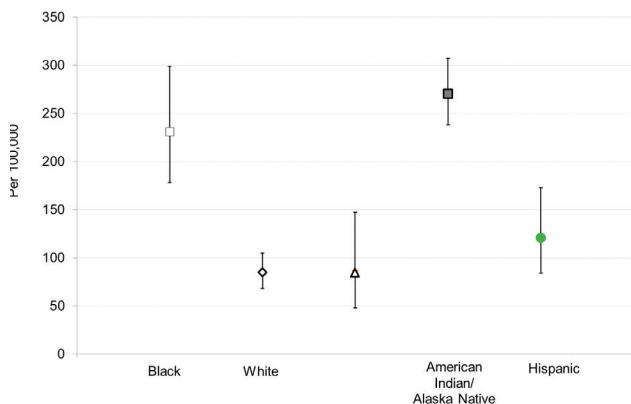
The social construct of race and ethnicity represents the lived experience of individuals in those groups. For individuals in racial and ethnic groups that are marginalized, this experience may involve discrimination as a result of structural racism (Bailey et al., 2021).

Emerging data show an association between psychological stress and biological changes, including epigenetic changes that predispose to chronic inflammation and the development of autoimmune diseases (Fagundes et al., 2013; Miller et al., 2011). For example, stress that resulted from exposure to systemic racism was shown to be associated with greater disease activity and organ damage in Black women with SLE (Chae et al., 2019; Martz et al., 2019).

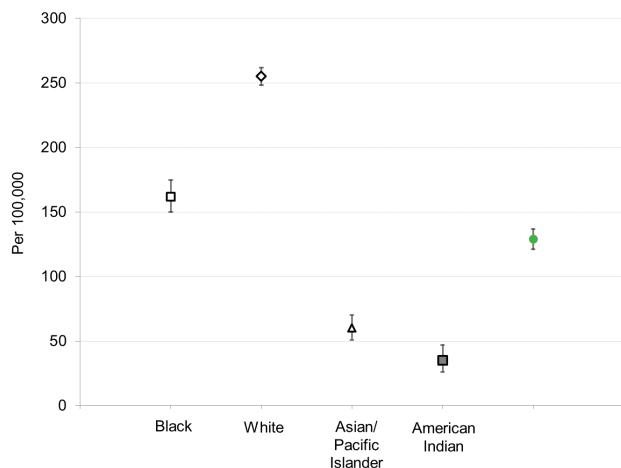
The role of race and ethnicity in the incidence, prevalence, and evolution of autoimmune diseases is therefore likely representative of epigenetic factors from a lived experience, overlaid on genetic susceptibility as a result of ancestry, which may only partially align with race and ethnic categorization (Miller et al., 2011; Sankar et al., 2004). Therefore, in research of autoimmune diseases, and human diseases more broadly, race and ethnicity cannot serve as a proxy for genetics.

Figures drawn based on data from

**A. Systemic Lupus Erythematosus**



**B. Type 1 Diabetes**

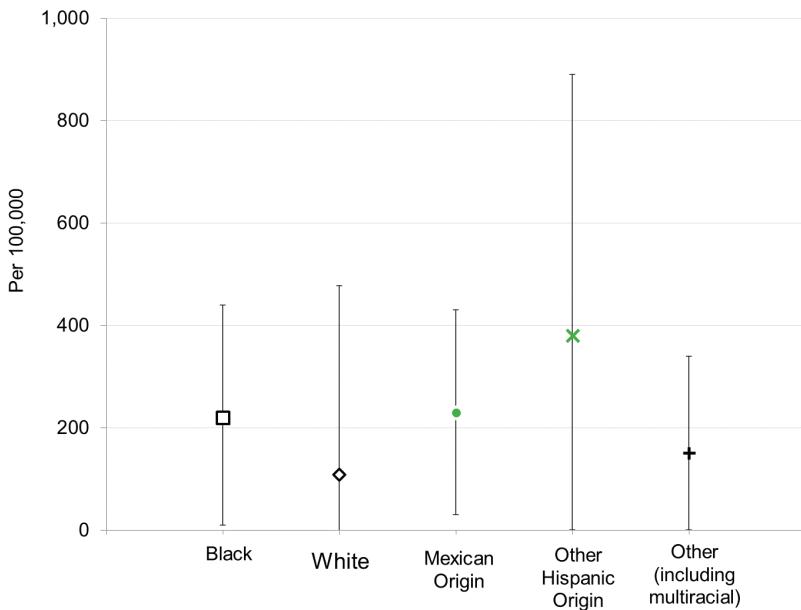
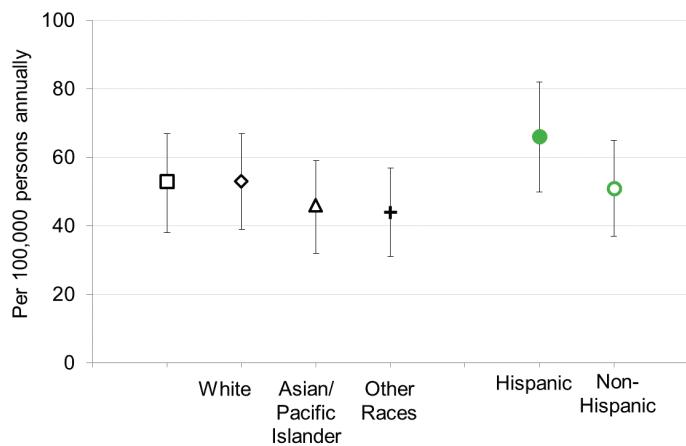


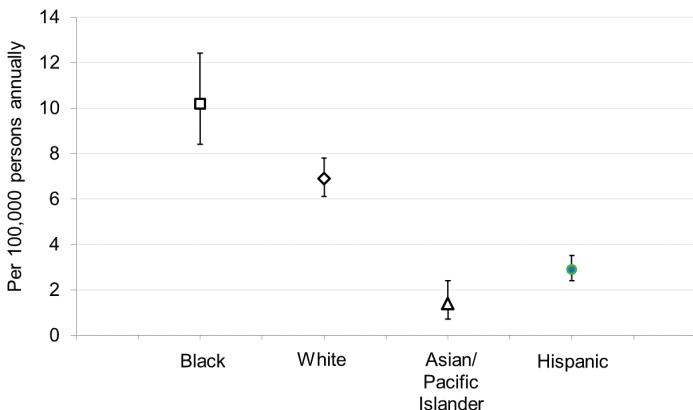
**FIGURE 2-3** Variability in disease rates in the United States by race or ethnicity. A. Prevalence of systemic lupus erythematosus (females). B. Prevalence of type 1 diabetes (age < 20). C. Prevalence of celiac disease (positive serology, age > 5). D. Incidence of rheumatoid arthritis (age > 18) (Kawatkar et al., 2019). E. Incidence of multiple sclerosis.

NOTE: Per 100,000 person-years = annually per 100,000 persons.

SOURCES: Figure A. created based on data drawn from Izmirly et al., 2021b; Figure B. created based on data drawn from Dabelea et al., 2014; Figure C. created based on data drawn from Mardini et al., 2015; Figure D. created based on data drawn from Kawatkar et al., 2019; Figure E. created based on data drawn from Langer-Gould et al., 2013.

*continued*

**C. Celiac Disease****D. Rheumatoid Arthritis****FIGURE 2-3** Continued

**E. Multiple Sclerosis****FIGURE 2-3** Continued

2021; Sankar et al., 2004). These barriers can be geographic (e.g., availability of services in rural areas), economic, and rooted in sociocultural experiences that can result in mistrust of medicine or medical services.

The previous discussion has highlighted diseases with moderate to strong predominance in women and diseases with increased risk in racial and ethnic minority populations. Within the full spectrum of autoimmune diseases, however, many other autoimmune illnesses do not reflect this pattern. Differences in the incidence or severity of diseases across demographic groups may have important implications for diagnosis and management of disease and may implicate the importance of genetic susceptibility in conjunction with environmental factors in disease pathogenesis. The committee believes that these striking variations in sex, race, and age patterns among autoimmune diseases are worthy of further research.

**Finding:** There is a lack of population-based data from diverse populations to accurately assess the incidence, prevalence, lifetime risk, epidemiologic trends, and the extent of the impact of autoimmune diseases on the U.S. population. In addition, existing data may not distinguish sex and gender. The best available long-term data are from a relatively racially and socioeconomically homogenous population, thereby limiting its application for understanding the variation

in genetic susceptibility and the variety of exposures, experiences, and socioeconomic drivers of autoimmune diseases.

*Conclusion: There is a need for population-based epidemiology studies that can provide the basis for studying numerous autoimmune diseases over at least a 20-year period. This resource could collectively provide a picture of the impact of these diseases in all groups representative of the U.S. population, and investigators could use it to facilitate the kind of population-based research needed to fully understand the development and prognosis of these diseases.*

### Coexisting Autoimmune Diseases

Historically, medical management occurring in subspecialties according to the organ system involved may have obscured associations between autoimmune diseases. However, shared features among certain autoimmune diseases is so well recognized, particularly within rheumatology, that nomenclature distinguishes between disease that is primary (stand-alone) or secondary to another autoimmune condition. In one study, a second diagnosable autoimmune disease occurred in 52 percent of those diagnosed with Sjögren's disease, 43 percent of those with antiphospholipid syndrome, 38 percent of those with SLE, and 30 percent of those with rheumatoid arthritis (Lockshin et al., 2015). The terms "primary" and "secondary" are misleading, however, since no evidence exists to support the hypotheses that one autoimmune disease precedes, causes, or dominates the other, or even that they are independently diagnosable illnesses. The appropriateness of such terminology was recently reviewed for Sjögren's disease (Kollert and Fisher, 2020), but the concepts discussed apply to other autoimmune diseases as well. Thus, the designation of "primary" or "secondary" has largely fallen out of favor.

In the medical literature, definitions of terms such as "comorbidity" and "complication" can be fluid and overlapping (Valderas et al., 2009). That much remains unknown about autoimmune diseases further complicates the use of precise definitions. For the purpose of this report, the committee uses the definitions provided in Box 2-3.

Abundant anecdotal evidence and case series of autoimmune disease clustering, beyond the classically described "overlap" conditions, has prompted research addressing whether co-occurrence of selected autoimmune diseases occurs within individuals and families at higher rates than expected by chance (Somers et al., 2006). Investigators have not studied all combinations of autoimmune diseases at the population level, and key studies on autoimmune coexistence within individuals have focused largely on multiple sclerosis, rheumatoid arthritis, autoimmune

**BOX 2-3**  
**Definitions Used in This Report for Conditions Coexisting With an Autoimmune Disease**

**Complication:** A coexisting condition, disease, or illness that is a direct result of the autoimmune disease or its treatment.

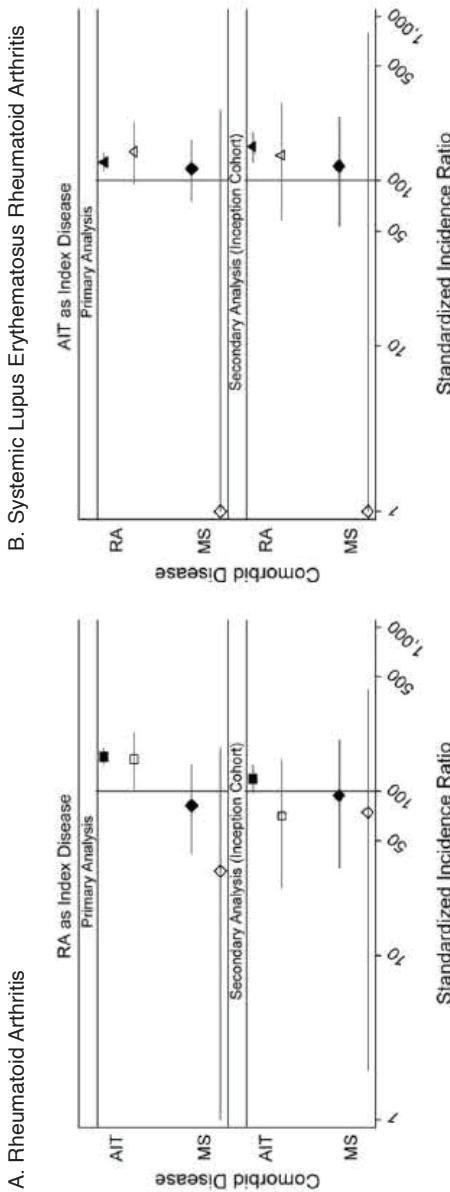
**Comorbidity:** A coexisting non-autoimmune illness.

**Co-occurring autoimmune disease:** A coexisting autoimmune disease that does not share symptoms or laboratory test results with the index autoimmune disease.

**Overlapping autoimmune disease:** Illness that exhibits clinical and laboratory test features of multiple autoimmune diseases.

thyroiditis (Hashimoto's thyroiditis), type 1 diabetes, IBD, and vitiligo as index conditions (Cooper et al., 2009). Overall, data support the idea that intra-person co-occurrence does occur at greater than expected rates for several combinations of autoimmune disease. For example, two large studies—one examining Kaiser Permanente Health Plan records and another examining two U.S. medical claim data sets—found that persons diagnosed with IBD had a significantly increased risk of developing multiple sclerosis, psoriasis or psoriatic arthritis, and rheumatoid arthritis compared with persons without an IBD diagnosis; moreover, the second study also found an increased risk of developing ankylosing spondylitis (Cohen et al., 2008; Weng et al., 2007).

A major epidemiologic study in the United Kingdom investigated the co-occurrence of four autoimmune conditions within individuals—multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and autoimmune thyroiditis (Somers et al., 2009). After controlling for age and calendar year, this study documented increased co-occurrence between rheumatoid arthritis, autoimmune thyroiditis, and type 1 diabetes compared with population expected rates, regardless of diagnostic sequence; sex-specific results were consistent with the overall findings (Figure 2-4). The magnitude of association was most prominent for autoimmune thyroiditis among patients with type 1 diabetes, in which risk was more than four times that expected. A notable exception to the premise of clustering was between multiple sclerosis and rheumatoid arthritis, where findings suggested an inverse association. Importantly, this study predicated the availability in the United Kingdom of tumor necrosis factor inhibitors, used today to treat some autoimmune diseases, which otherwise could have confounded results given reports of multiple sclerosis in association



**FIGURE 2-4** Sex-specific standardized incidence ratios and 95% confidence intervals for the existence of coexisting autoimmune diseases within each index disease category (a standardized incidence ratio of 100 indicates unity). For disease combinations for which no coexisting cases were observed and the standardized incidence ratio was consequently zero, the point estimate is graphed with the value of 1 to conform to the log scale, and a 1-tail, 97.5% confidence interval is presented. Solid symbols (▲): females; hollow symbols (□): males. Coexisting autoimmune diseases: (▲ / △): rheumatoid arthritis; (■ / □): autoimmune thyroiditis; (● / ○): multiple sclerosis.

NOTE: AIT, autoimmune thyroiditis; ANCA, anti-neutrophil cytoplasmic autoantibody; IDDM, insulin-dependent diabetes mellitus; MS, multiple sclerosis; RA, rheumatoid arthritis.

SOURCE: Somers et al., 2009.

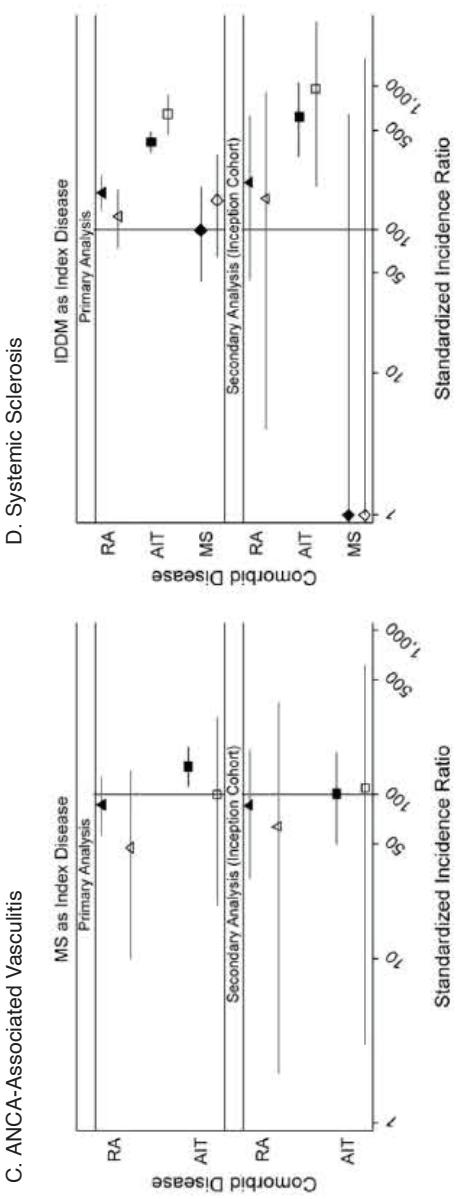


FIGURE 2-4 Continued

with such treatment. An inverse association between multiple sclerosis and rheumatoid arthritis was also supported by a pair of Danish studies of individuals and families (Eaton et al., 2007; Nielsen et al., 2008) and within families based on a systematic review (Somers et al., 2006). A broader implication is that characterization of baseline rates of coexistence provides important context for interpreting pharmacovigilance data as immunotherapy options continue to expand (Somers et al., 2009).

Family studies have also reported increased occurrence of autoimmune diseases among first degree relatives of case versus control individuals. Aside from the combinations of autoimmune diseases detected within individuals described above, additional disease associations reported in family studies include polyarteritis nodosa, Addison's disease, Crohn's disease, and "autoimmune diseases in general" in relatives of individuals with multiple sclerosis; autoimmune thyroid diseases and "autoimmune diseases in general" for SLE; "autoimmune diseases in general" for Sjögren's disease; and autoimmune thyroid diseases and "autoimmune diseases in general" for idiopathic inflammatory myopathy (Cooper et al., 2009).

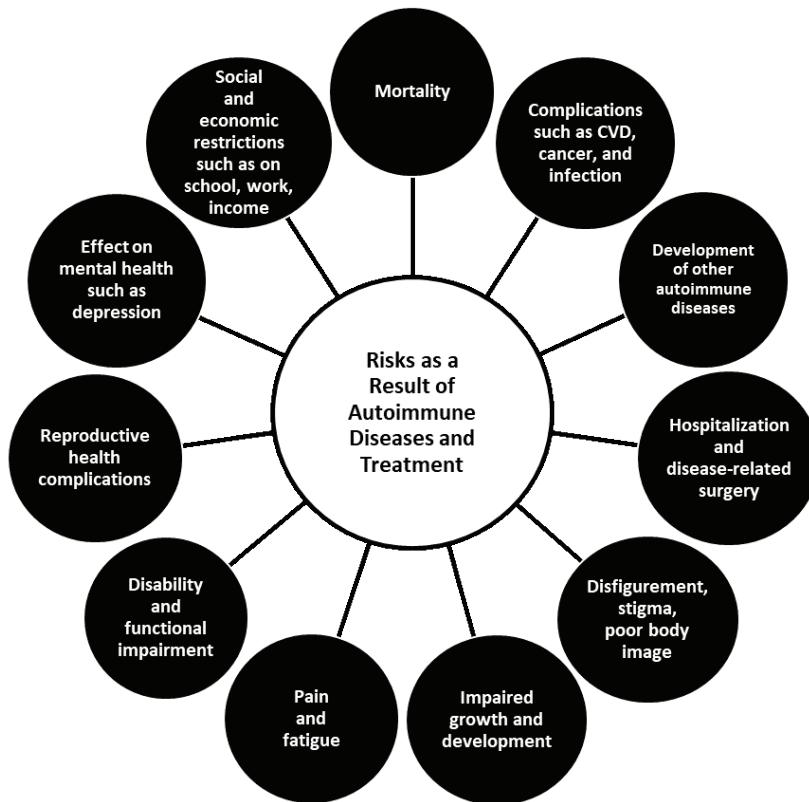
**Finding:** Limited data exist on the presence of co-occurring autoimmune diseases in individuals, and the studies have concentrated on comparatively few autoimmune diseases when measured against the large number of diseases generally accepted as being autoimmune diseases.

*Conclusion: Additional research is needed to identify the patterns of a broad range of co-occurring autoimmune diseases as this could provide important context for interpreting pharmacovigilance data and provide insight into underlying biologic mechanisms that could inform strategies for the prevention, early diagnosis, and treatment of subsequent autoimmune diseases in individuals with autoimmune disease.*

### Morbidity, Mortality, and Quality of Life

The manifestations and consequences of autoimmune diseases vary depending on the target organs or systems. It is important to view the effects of autoimmune diseases not just through a lens directed at physical health, but through one that also views elements such as normal social interaction and development, mental health, the ability to gain an education and pursue employment, and the capacity to have children, all of which can affect quality of life (Figure 2-5).

For some autoimmune diseases, acute effects can be severe. Undiagnosed or inadequately controlled type 1 diabetes, for example, can lead to



**FIGURE 2-5** Effects of autoimmune diseases and treatment.

NOTE: CVD, cardiovascular disease.

diabetic ketoacidosis, coma, and death. SLE has a relatively high mortality rate and a significant racial disparity in mortality, and mortality risk is significantly elevated compared with expected rates (standardized mortality ratios, 2 to 5 times higher) (Gianfrancesco et al., 2021; Jorge et al., 2018). Ten-year mortality rates in an incidence cohort of SLE in Georgia were 28 percent in Black persons and 9 percent in White persons (Lim et al., 2019). In other autoimmune diseases, absolute and relative mortality risks are lower. A meta-analysis of 35 studies of IBD reported a standardized mortality ratio of 1.08 (95 percent confidence interval 0.97–1.21) in inception cohorts of ulcerative colitis and 1.34 (95 percent confidence interval 1.15–1.56) in inception cohorts of Crohn's disease (Bewtra et al., 2013).

For many autoimmune conditions, the underlying disease process, including a chronic inflammatory response and/or the long-term use of immunosuppressant drugs, results in increased risks of infectious disease

(bacterial, viral, mycobacterial, and fungal) as well as cardiovascular disease. For example, an elevated risk of cardiovascular disease, including coronary revascularization procedures, myocardial infarction, peripheral vascular disease, and cardiovascular deaths, occurs for rheumatoid arthritis, systemic sclerosis, and SLE (Kremers et al., 2008; Kurmann et al., 2020; Man et al., 2013; McMahon et al., 2011). The concept of accelerated atherosclerosis associated with autoimmune disease is key to understanding the increased risk of cardiovascular disease seen even at relatively young ages (under 45 years of age), and the evaluation and control of cardiovascular risk factors is a vital component of clinical care for autoimmune diseases (Durante and Bronzato, 2015).

Autoimmune diseases are also associated with specific types of cancer, and there is a need for a better understanding of pathogenic mechanisms in these individuals as well as optimal patient care. One study using the SEER database found that Sjögren's disease, rheumatoid arthritis, SLE, and autoimmune hemolytic anemia were associated with a 1.5- to 2-fold increased risk of three or more types of lymphomas, while psoriasis, pemphigus, and discoid lupus erythematosus were associated with a 3- to 6-fold increased risk of T-cell non-Hodgkin lymphoma (Anderson et al., 2009; Chiesa Fuxench et al., 2016).

Some autoimmune diseases are also associated with increased cancer risk at specific sites related to the disease. For example, people with IBD have an increased incidence of colorectal and other gastrointestinal cancers (Axelrad et al., 2016). The role of chronic inflammation, prolonged use of immunosuppressant agents, and common risk factors—as in the case of rheumatoid arthritis and lung cancer (Simon et al., 2015)—are important avenues for future research into cancer risk and autoimmune disease. In addition, much remains to be learned about how best to treat patients with autoimmune disease and cancer. Until recently, for example, patients with autoimmune disease and cancer were excluded from clinical trials of immunotherapy, which increases the immune system's capability to detect and kill tumor cells, because of concerns that the drugs might increase autoimmunity and possibly cause severe and life-threatening complications (NLM, 2021).

Flare-ups of symptoms or disease activity, often requiring hospitalization, are common in many autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, SLE, and IBD (Morales-Tisnes et al., 2021; Panopalis et al., 2012). The remitting-relapsing course of these diseases can be challenging to manage from a medical as well as a social and psychological perspective. In addition, the damage caused by some autoimmune diseases, such as vasculitis, SLE, and PBC, may require organ transplantation (Albuquerque et al., 2019; Carey et al., 2015; Jain et al., 2021).

Pain is a common symptom in many autoimmune diseases although the etiology varies. For example, owing to nerve involvement or damage in multiple sclerosis, individuals with the disease often experience spasticity with stiffness, flexor spasms, and uncontrollable muscle contractions as well as the burning sensations of dysesthesias and facial pain due to the severe stabbing-like *tic douloureux* (IOM, 2001). The chronic inflammation in rheumatoid arthritis causes progressive joint deterioration and secondary osteoarthritis, leading to pain and stiffness; while up to 90.4 percent of patients with the disease seek health care for severe pain, pain-management options remain limited (Sanchez-Florez et al., 2021). Persons with IBD often experience joint and spinal pain from inflammatory arthritis, in addition to abdominal and pelvic pain; in those with perianal disease from fistulae, pain can be severe. Moreover, pain is a risk factor for depression, anxiety, and disability in individuals with IBD (van der Valk et al., 2014a).

One of the most common complaints among individuals with autoimmune diseases is fatigue, which in this context is particularly complex and variable because it is likely linked to differing causal mechanisms. Multiple physiological processes may contribute to fatigue in autoimmune diseases including inflammatory activation of the immune system that affects the peripheral and central nervous systems (Lee and Giuliani, 2019b; Morris et al., 2015). Fatigue can be debilitating, impede performance of even simple daily tasks, and contribute to mental health problems such as depressed mood (Zielinski et al., 2019). When fatigue prevents people from fulfilling normal social roles or holding a job, it can cause isolation, impose financial burdens on them and their families, and decrease quality of life. There are currently no long-lasting interventions to effectively treat fatigue in persons with autoimmune diseases (Zielinski et al., 2019).

Autoimmune disease can have impacts on physical function. Neurological effects in multiple sclerosis include vision impairment and problems with balance and mobility, some being severe, and these effects are highly important to people living with this condition (Heesen et al., 2008). Blindness resulting from retinopathy is one of the most common complications of type 1 diabetes (James et al., 2014). In addition, the lesions and scarring that can result from skin manifestations of some diseases, such as psoriasis, can result in disfigurement and stigmatization (van Beugen et al., 2017). All of these effects can act to isolate a person physically and/or psychologically, impede social relationships, and restrict access to education and employment. Measures focusing on health care utilization may, in fact, overlook the significant effects of autoimmune diseases.

Children with autoimmune diseases are at risk for adverse impacts on growth and development as a result of the diseases and their treatment.

Growth failure, as indicated by height velocity and final height that rank below age- and sex-expected percentile norms, can be caused by the effects on bone growth of chronic systemic inflammation as well as glucocorticoid therapy. Inflammation may also cause delayed puberty, which may adversely impact peak bone mass and linear growth (Kao et al., 2019). Studies in individuals with childhood-onset SLE have found that about 15 percent experience low height velocity (Bandeira et al., 2006; Gutierrez-Suarez et al., 2006), that the average final height is lower than target height, a calculation based on the heights of the parents (Heshin-Bekenstein et al., 2018), and that these effects are most marked in those experiencing pre-menarche disease onset (Sontichai et al., 2020). A recent large cohort study found that 10 percent of children with the systemic form of juvenile idiopathic arthritis had short stature (Guzman et al., 2017). However, some children with autoimmune disease experience a period of catch-up growth when their disease responds to treatment and / or glucocorticoid therapy is reduced (Gutierrez-Suarez et al., 2006; Guzman et al., 2017). Growth hormone therapy also may mitigate adverse growth effects (Simon and Bechtold, 2009). Development of new effective glucocorticoid-sparing medications may lessen adverse effects on growth and development for children with autoimmune diseases.

In young adults and during the reproductive years, autoimmune diseases can generate additional risks and complications (Sammaritano et al., 2020). Pregnancy or the post-partum period may worsen the course of autoimmune diseases, or the disease itself may result in increased risk of adverse pregnancy outcomes, including spontaneous abortion. This can lead to the need to make difficult choices regarding the use of disease-modifying medications during pregnancy. Those wishing to have children may have to consider the potential effects of treatments on fertility or carrying a pregnancy to term, and consider options for oocyte preservation.

Another effect of autoimmune diseases, particularly during the young and middle-aged adult years, is employment-related disability. Studies of people with IBD, multiple sclerosis, psoriasis, rheumatoid arthritis, systemic sclerosis, and SLE report partial or full work disability, with one cohort study of persons with early rheumatoid arthritis observing a work disability rate of 28 percent at study start and 44 percent 15 years later (Eberhardt et al., 2007; Orbai et al., 2021; Raggi et al., 2016; Scofield et al., 2008; Sharif et al., 2011; van der Valk et al., 2014b). The relapsing-remitting nature of these diseases, as well as some of the features that contribute to disability such as fatigue and pain, may result in additional challenges to receiving disability benefits (Scofield et al., 2008). The indirect costs of lost productivity represent approximately 30 percent of the estimated total costs of rheumatoid arthritis (Birnbaum et al., 2010) and psoriasis (Vanderpuye-Orgle et al., 2015) in the United States, and approximately

50 percent of the total costs of IBD during the first year after diagnosis among working-age people in Sweden (Khalili et al., 2020).

Within the sphere of mental health, depression or depressive symptoms are common among people living with autoimmune diseases and can contribute to the risk of reduced employment (Eckert et al., 2017; Kurd et al., 2010; Moustafa et al., 2020; Vanderpuye-Orgle et al., 2015). In some diseases, research has not ruled out the possibility that the direct central nervous system effects of rheumatoid arthritis, SLE, and multiple sclerosis may play a role in inducing depression (Vallerand et al., 2018, 2019). In addition, difficulties with mobility, the challenges of working while coping with disease flares, and the physical effects of specific diseases that produce visible damage to skin or joints are consequences of autoimmune diseases that can significantly contribute to social isolation and affect quality of life. The directionality of effects of inflammation, depression, fatigue, and disease expression is an area requiring additional research (Lee and Giuliani, 2019a; Vallerand et al., 2018).

**Finding:** Autoimmune diseases are associated with an increased risk of cancer.

*Conclusion: Additional research is needed to characterize the roles of chronic inflammation, prolonged use of immunosuppressant agents, and common risk factors in increased cancer risk in persons with autoimmune disease. In addition, there is a need for research to obtain a greater understanding of how best to treat patients with autoimmune disease and cancer.*

**Finding:** Fatigue and depression or depressive symptoms commonly occur in individuals with autoimmune diseases; their etiology is unclear. There are no long-lasting treatments for fatigue. Both can greatly affect quality of life.

*Conclusion: Additional research is needed to understand the directionality of effects of inflammation, depression, fatigue, and disease expression in persons with autoimmune diseases.*

#### *Estimates of Economic Impact*

Few studies have estimated the direct and indirect costs of specific autoimmune diseases in the United States, and the committee is not aware of any studies attempting to estimate the overall costs of these conditions. The limited information that is available on the economic impact of specific autoimmune diseases is discussed above and in Chapter 3. The available evidence, while limited in scope, supports the notion that the

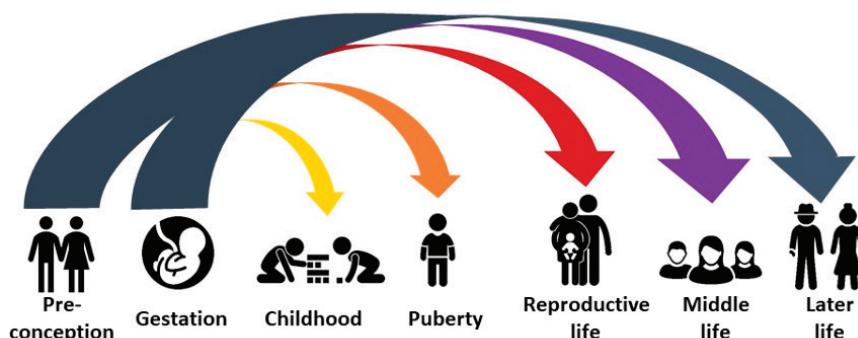
direct and indirect costs of autoimmune diseases can be high (Adelman et al., 2013; Birnbaum et al., 2010; Vanderpuye-Orgle et al., 2015).

**Finding:** There are little data on the direct and indirect costs in the United States of specific autoimmune diseases and of autoimmune diseases overall.

### THE LIFE-COURSE FRAMEWORK AND AUTOIMMUNE DISEASES

The life-course framework for health research is highly relevant for the study of autoimmune diseases. This framework emphasizes understanding how early life exposures—factors such as environmental toxicants or psychological stressors that are associated with an outcome—and timing of these exposures influence health along the life stages (Ben-Shlomo and Kuh, 2002; Jacob et al., 2017; Liu et al., 2010; Lynch and Smith, 2005), both at a population and individual patient level. This approach highlights the importance of conceptualizing autoimmune diseases as a result of social and environmental factors, or exposures, experienced at different points, from the *in utero* period, through childhood and adolescence, and on to young, mid-, and older adulthood (Figure 2-6).

Examples of environmental exposures are toxicants and viruses, and examples of social exposures are stressors such as poverty, abuse, and discrimination. The multidisciplinary life-course framework enables examination of how these social and environmental determinants of health throughout the life stages can differentially affect biological processes to influence the development and the course of chronic diseases. For



**FIGURE 2-6** Exposures across the lifespan impact life-long health, which highlights the importance of a life-course approach to health.

SOURCE: Adapted with permission from National Institute of Environmental Health Sciences.

example, data from the longitudinal World Trade Center Health Registry show an increased risk for developing systemic autoimmune disease following exposure to dust and traumatic experiences from the September 11, 2001, terrorist attack (Miller-Archie et al., 2020). Additionally, data from the Nurses' Health Study II, a large longitudinal cohort of U.S. female nurses, show an increased risk of developing SLE in those with exposure to childhood physical and emotional abuse (Feldman et al., 2019).

The epidemiologic study of autoimmune diseases using a life-course framework emphasizes a longitudinal approach inclusive of all life stages, linking a multiplicity of exposures across the life course to later health outcomes. It also emphasizes attention to the inter-relationships of these exposures and vulnerable developmental time periods. For example, findings from the National Institute of Environmental Health Sciences-funded Sister Study Cohort (Parks et al., 2016) showed that the early life factors of preterm birth and childhood pesticide exposure were associated with development of SLE in adulthood. Additional aspects for chronic autoimmune diseases in particular include the fluctuation of disease activity over periods of flare and remission, as well as the accumulation of permanent organ damage over time resulting from inflammation. Accounting for these complexities often presents methodological challenges for modeling repeat observations, hierarchical data, latent exposures, and multiple interactive effects (Kuh et al., 2003). Researchers have used complex analytic models, such as multi-level models, latent growth models, and Markov models in studying chronic diseases, and they are highly useful for understanding complex autoimmune diseases.

While researchers have applied the life-course framework to the epidemiologic study of populations, it is also useful for studying disease at the individual level (Halfon and Hochstein, 2002). Measuring the effect of socio-environmental factors on individuals with autoimmune disease across time and critical developmental periods increases the understanding of disease mechanisms, trajectories, and heterogeneity. This is of particular relevance to studying autoimmune diseases because they typically evolve over time, and a given disease can manifest differently from patient to patient. To understand the mechanisms underlying development and course of autoimmune diseases, it is important to characterize changes in biologic structure and function across the lifespan, and how genetic, social, and environmental factors cause deviation in expected biologic trajectories of typical development (Hardy and O'Neill, 2020). These trajectories may be non-linear, reflecting critical exposure periods, differential impacts across time and biologic structures, and the biologic impact of cumulative exposures. To increase knowledge of autoimmune disease and develop treatments, long-term systems for data collection

and complex analytic approaches are necessary to model these aspects of disease mechanisms and trajectories within and across individuals and to elucidate the heterogeneity present within diseases.

Several implications arise from incorporating a life-course approach for studying autoimmune diseases:

- This approach requires longitudinal studies that incorporate children and adult populations, with particular attention to critical life periods for the effects of inflammation and disease damage.
- Methodological expertise is critical for modeling the issues of time, timing, and inter-relationship of exposures in relation to disease mechanisms and outcomes.
- A team science approach is key to bringing together multidisciplinary expertise in genetics and biology, social and environmental factors, life stages, and other relevant knowledge areas.
- Although the life-course approach involves epidemiology at the population level, it is also relevant to understanding disease processes at the individual patient level. It therefore provides understanding of opportunities for development of clinical treatments and behavioral interventions, as well as policy changes aimed at both prevention and provision of interventions.

**Finding:** A life-course approach to the epidemiological study of autoimmune disease could involve longitudinal studies that incorporate children and adult populations, enable modeling of the issues of time, timing, and inter-relationship of exposures in relation to disease mechanisms and outcomes, and engage multidisciplinary expertise in genetics and biology, social and environmental factors, life stages, and other relevant knowledge areas. Such an approach could better characterize the disease processes of autoimmune diseases, conditions that can affect individuals at any age and that are chronic, heterogeneous, and may involve flare and remission.

## SUMMARY AND RESEARCH IMPLICATIONS

Autoimmunity arises when the immune system fails to distinguish self from non-self. This can result, over time, in disease conditions involving pathological tissue damage caused by autoreactive T cells and auto-antibodies. Both the innate and adaptive immune systems are involved in promoting autoimmune disease, and genetics, social and environmental exposures, and sex differences may contribute to the development or exacerbation of autoimmune diseases.

There is no consensus definition of autoimmune disease. For more than 50 years, clinical criteria such as specific autoantibodies and symptoms have been used to characterize and classify autoimmune diseases. More recently, insights from research on biologic mechanisms have revealed commonalities between autoimmune diseases and autoinflammatory diseases, as well as other diseases that are not considered to be autoimmune diseases, making the definition less clear-cut. The two different approaches to characterize and understand autoimmune diseases each have advantages. Defining autoimmune diseases according to biological mechanisms may be useful in developing interventions and treatment, particularly when the mechanisms are shared across diseases. Characterizing autoimmune diseases by clinical phenotype alone, however, can impact patient care and impede research. An atypical presentation of an autoimmune disease, for example, could slow its diagnosis and treatment, or result in the person with the disease being excluded from a clinical trial when their inclusion might provide insight into the disease.

Incidence and prevalence data for autoimmune diseases in the United States are limited and not easily accessible. The last study that considered the prevalence of autoimmune diseases as a whole in the United States estimated a 7.6 to 9.4 percent prevalence of these conditions, but the study focused on just 29 autoimmune diseases and was published more than a decade ago (Cooper et al., 2009). Among the most common autoimmune diseases are celiac disease, rheumatoid arthritis, psoriasis, IBD, and type 1 diabetes. A critical limitation is the lack of population-based data from diverse populations that would enable researchers to accurately assess the incidence, prevalence, lifetime risk, and epidemiologic trends of autoimmune diseases in the U.S. population as well as extent of their impact.

Many, but not all, autoimmune diseases predominantly affect women, with some female-to-male incidence ratios equaling 6:1 or greater. Exceptions include type 1 diabetes and myocarditis, which occur more often in males (Coronado et al., 2019; Fairweather et al., 2013). No single pattern of racial and ethnic disparities is seen in incidence or prevalence among autoimmune diseases; for some conditions, the highest rates occur among Black, American Indian, and Alaska Native populations, while for others, the highest rates occur in White populations (Izmirly et al., 2021b). Researchers have also observed disparities in the severity and prognosis of autoimmune diseases according to race and ethnicity (Barton et al., 2011; Lim et al., 2019; Ventura et al., 2017). Research is needed to identify the reasons for these and other disparities. Autoimmune diseases display varied age-of-onset patterns, with some occurring primarily in children, teens, and young adults, such as type 1 diabetes, and others occurring more commonly through adulthood or reaching the highest incidence after age 60, such as primary Sjögren's disease.

Autoimmune diseases are heterogeneous and long-lasting conditions. The impact on physical health—which can include pain and fatigue, an increased risk of developing a wide variety of other conditions, impaired growth and development, disfigurement, disability, functional impairment, and death—is substantial. Having an autoimmune disease may carry an increased risk of cancer (Anderson et al., 2009; Axelrad et al., 2016; Chiesa Fuxench et al., 2016); research is needed to establish how best to treat the patient. Autoimmune diseases can have adverse effects on social interaction and development, mental health, the capacity to have children, and education and employment.

Economic-impact research is inadequate, but available data indicate that the direct and indirect costs of autoimmune diseases can be high. Accurate mortality data are also lacking, one reason being that death certificates may not provide complete information on the autoimmune disease that contributed to death (Calvo-Alén et al., 2005; Molina et al., 2015).

The study of co-occurring autoimmune diseases in individuals has focused largely on multiple sclerosis, rheumatoid arthritis, autoimmune thyroiditis, type 1 diabetes, and IBD, with several combinations occurring at greater than expected rates. A broader understanding of the patterns of coexisting autoimmune diseases, as well as of their underlying biologic mechanisms, could inform strategies for the prevention, early diagnosis, and treatment of subsequent autoimmune diseases in individuals with one autoimmune disease.

Finally, applying a life-course, multidisciplinary framework to longitudinal epidemiologic studies that include children and adults could provide insight into issues involving exposures and timing that play a role in the etiology, mechanisms, and course and outcomes of these highly variable diseases.

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## Overview of Select Autoimmune Diseases

As noted in Chapter 1, the committee focused a literature review on a select number of autoimmune conditions. These autoimmune diseases—Sjögren's disease, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis, psoriasis, inflammatory bowel disease (IBD), celiac disease, primary biliary cholangitis (PBC), multiple sclerosis, type 1 diabetes, and autoimmune thyroid disease—serve as representatives of this heterogeneous class of disorders. As explained at greater length in Chapter 1, the committee included diseases that are overrepresented in women, affect multiple systems, and are associated with coexisting morbidity. The committee selected diseases that collectively can represent the spectrum of autoimmune diseases. The committee also took into account the congressional language requesting the study and the availability of data to assess the National Institutes of Health (NIH) research portfolio.

There are no known cures for autoimmune diseases. Autoimmune diseases may affect any part of the body and sometimes affect many parts or result in systemic features. Classically, autoimmune diseases have been organized or named based on the organ system or tissue affected, and health care providers specializing in areas of medicine that focus on those organ systems are typically the ones who diagnose and manage these diseases. However, the specific mechanisms that dictate which organ an autoimmune disease affects when it develops are not fully understood, and many similarities, including genetic susceptibility and disease mechanisms, exist among autoimmune diseases that affect different organ systems.

While an immune response that targets different organ systems or self-antigens characterizes each disease, classifying diseases by clinical manifestations and laboratory tests that detect autoantibodies, for example, may not be the most accurate way to guide therapeutic decision making, given that the presence of similar clinical manifestations or autoantibodies can result from different immunological mechanisms. For example, a recent study of seven systemic autoimmune diseases—Sjögren's disease, SLE, APS, rheumatoid arthritis, systemic sclerosis, mixed connective tissue disease, and undifferentiated connective tissue disease—reported complex gene expression and epigenetic analyses that enabled the investigators to arrange these seven diseases into four different molecular clusters, with each disease represented across all four clusters (Barturen et al., 2021). Three clusters represented three different pathologic immunological pathways and mechanisms associated with disease activity, while the fourth “undefined” cluster was more similar to that of healthy controls. Over time, most individuals remained within their original cluster or alternated between their original pathologic cluster and the undefined/healthy-control-like cluster. The authors suggest that defining such clusters may help to guide therapies that are more likely to effectively modulate the immune pathways most relevant for a given individual's autoimmune disease manifestations. Similarly, cluster analysis may predict the trajectory of rheumatoid arthritis (RA-MAP Consortium, 2021).

In this chapter, the committee provides an overview of select autoimmune diseases to highlight the complexities of autoimmune diseases, and it has structured the review of each disease to reflect the committee's charge as directed in the statement of task for this study. To illustrate some common complexities—including heterogeneity, targeting of ubiquitous self-antigens, and an absence of adequate diagnostic biomarkers or effective therapies—the chapter begins with Sjögren's disease, a systemic autoimmune disease that has some organ-specific features, is most commonly diagnosed in women, and often co-occurs with other autoimmune diseases. After Sjögren's disease, the chapter will provide information on three systemic autoimmune diseases—SLE, APS, and rheumatoid arthritis—followed by discussions on autoimmune diseases that affect a specific tissue or organ system, including the skin (psoriasis), the gastrointestinal system (IBD, celiac disease, and PBC), the central nervous system (CNS) (multiple sclerosis), and the endocrine system (type 1 diabetes and autoimmune thyroid disease).

Chapter 2 provides data on the incidence and prevalence of these diseases, and this chapter provides information on sex, age, racial, and ethnic disparities. In addition, Appendix D provides more detailed epidemiologic information for each disease.

## SJÖGREN'S DISEASE

Sjögren's disease (often referred to as Sjögren's syndrome, though the term syndrome is less accurate) is a chronic autoimmune disease with organ-specific and systemic features (Baer and Hammitt, 2021). Sjögren's disease has no well-defined treatments to slow the autoimmune process (Vivino et al., 2019), which can negatively affect an individual's quality of life (Cornec et al., 2017; McCoy et al., 2021; Saldanha et al., 2020; Sivakumar et al., 2021). The classic features of Sjögren's disease include dryness of the mouth and eyes that results from a progressive autoimmune attack directed toward the saliva-producing (salivary) and tear-producing (lacrimal) glands. The consequences of this attack range from discomfort to vision-threatening ocular damage, loss of teeth resulting from extensive dental caries, and difficulty carrying out common activities such as chewing, swallowing, and talking. Sjögren's disease often causes dryness of other parts of the body in addition to the mouth and eyes, including nasal mucosa (causing irritation and frequent nosebleeds), lower airways (causing chronic dry cough), skin (causing itchiness), and vaginal mucosa (causing general discomfort as well as pain during sexual intercourse and decreased sexual satisfaction) (Vivino et al., 2019). Besides providing moisture and lubrication, secretions from glands in these tissues help prevent infections, so gland dysfunction increases risk of infection.

Beyond dryness, many individuals with Sjögren's disease develop severe pain and fatigue. The pain may result from autoimmune inflammation of the joints (arthritis) or muscles (myositis), but more commonly it occurs without inflammation of the affected areas, making it more difficult to formally assess or treat. The fatigue that accompanies Sjögren's disease is also poorly understood and is difficult to treat. Together, dryness, pain, and fatigue contribute to functional disability, decreased work productivity, and overall decreased quality of life (Cornec et al., 2017; McCoy et al., 2021; Saldanha et al., 2020; Sivakumar et al., 2021; Vivino et al., 2019). In addition, Sjögren's disease may affect any organ either by direct autoimmune attack or as a result of circulating immune complexes depositing in an organ (Vivino et al., 2019). These extra-glandular manifestations may affect joints, muscles, blood cells, kidneys, lungs, skin, the nervous system, and the gastrointestinal system.

The slowly progressive dryness features may not lead an individual to seek medical care, though hormone changes associated with menopause greatly exacerbate the already developing dryness, prompting evaluation for Sjögren's disease. Earlier diagnosis may occur when other organs are affected, leading an individual to seek medical care for the extra-glandular manifestations. However, health care providers may fail to consider Sjögren's disease as a diagnosis when there is a lack of profound dryness

at presentation or when the main symptoms are musculoskeletal pain and fatigue.

### Epidemiology and Impact

Information on disparities in the epidemiology of Sjögren's disease can be found in Box 3-1.

#### **BOX 3-1 Sjögren's Disease: Sex, Age, Racial and Ethnic Disparities**

- The female-to-male ratio ranges from 6:1 in small U.S. studies (Izmirly et al., 2019; Maciel et al., 2017) to 14:1 in adults based in large global studies (Basiaga et al., 2020; Brito-Zerón et al., 2020; Ramos-Casals et al., 2020)
  - in the same global studies, the female-to-male ratio in children was 5:1
- Racial breakdown from a multinational study: 77 percent White, 14 percent Asian, 6 percent Hispanic, 1.4 percent Black (Brito-Zerón et al., 2020)
  - Native Americas are affected disproportionately with a higher risk of diagnosis and increased disease activity (Scofield et al., 2020)
  - measures of disease activity are highest in Black individuals, followed by White, Asian, and Hispanic individuals

### *Complications, Other Morbidity, and Long-Term Consequences*

Sjögren's disease commonly co-occurs with other autoimmune diseases. Among the autoimmune diseases that most often co-occur with Sjögren's disease are autoimmune thyroid disease, rheumatoid arthritis, SLE, systemic sclerosis, and autoimmune liver disease, including primary biliary cholangitis (Anaya et al., 2016). Beyond co-occurring autoimmune diseases, complications associated with Sjögren's disease include cardiovascular disease, lymphoma, and depression (Beltai et al., 2020; Ekström Smedby et al., 2008; Westhoff et al., 2012). Sjögren's disease autoimmunity confers a 4- to 10-fold increased risk of lymphoma (Ekström Smedby et al., 2008).

Together with the profound dryness, pain, fatigue, and other disease-specific effects described above, these complications and coexisting conditions contribute to the overall decrease in quality of life and work productivity and increase in health care cost in individuals with Sjögren's disease (Miyamoto et al., 2019). However, there are no reports in the literature of detailed studies on the life course of individuals with Sjögren's disease to more specifically define the contributions of each possible manifestation on life course.

In pregnant women with Sjögren's disease, anti-Sjögren's syndrome-related antigen A autoantibodies (SSA/Ro) autoantibodies associated with Sjögren's disease can cross the placenta and cause neonatal lupus in the developing fetus. While most neonatal lupus manifestations resolve without long-term consequences once the mother's antibodies have been cleared from the infant's circulation, the autoantibodies may damage the conduction system of the fetal heart, resulting in congenital heart block that causes severe reduction in fetal heart rate and may lead to fetal death or the need for pacemaker placement soon after birth (Brucato et al., 2011). Complete heart block occurs in only 1–2 percent of neonatal lupus cases, but the risk increases to 15 percent for subsequent pregnancies. The diagnosis of neonatal lupus in the baby often prompts initiating tests of the mother for Sjögren's disease-associated antibodies, and the formal diagnosis of Sjögren's disease, based on clinical findings rather than autoantibodies alone, may not occur for months to years later.

### *Economic Impact*

Disability, decreased work productivity, decreased quality of life, and direct health care costs contribute to the overall economic impact of Sjögren's disease (Uchino and Schaumberg, 2013). In the United States, a retrospective observational study using claims databases reported a 40 percent increase in all-cause health care costs in the year after diagnosis compared with the year prior to diagnosis (Birt et al., 2017). The average

cost during the first year following diagnosis of Sjögren's disease was \$20,416 per person. One study found similar economic impact in other countries (Miyamoto et al., 2019).

### Risk Factors and Etiology

The X chromosome plays a significant role in the risk of developing Sjögren's disease. Females with the standard chromosomal count have a greater risk than males with the standard chromosomal count. However, the prevalence of Sjögren's disease was approximately three times higher than in the general population among females with an extra X chromosome (Liu et al., 2016) and 15 times higher in males with an extra X chromosome (Harris et al., 2016). As in other systemic rheumatic diseases, genetic variants associated with Sjögren's disease are complex and include genes in the region of chromosome 6 that codes for human leukocyte antigens (HLA), as well as other genes associated with immune function (Imgenberg-Kreuz et al., 2021; Thorlacius et al., 2020).

Epigenetic modifications may also predispose an individual to develop Sjögren's disease (Imgenberg-Kreuz et al., 2019). Among environmental risk factors, studies have focused on microbial infections, such as Epstein-Barr virus (EBV), cytomegalovirus, and hepatitis C (Björk et al., 2020). Despite associations with different viral or bacterial infections, research has not established a causative role for infections in the development of Sjögren's disease. Studies have also implicated stress, low levels of vitamin D, and various organic chemical factors in the development of Sjögren's disease, but the data do not suggest clear associations with the disease (Björk et al., 2020).

As with other autoimmune diseases, the immune response targeting self-antigens in Sjögren's disease is complex. While the specific autoimmune mechanisms in Sjögren's disease are not fully understood, research has identified several antigens as targets of autoantibodies (Fayyaz et al., 2016; Martín-Nares and Hernández-Molina, 2019). For diagnostic purposes, the autoantibodies most commonly assayed include those often found in other autoimmune diseases, such as antinuclear antibodies and rheumatoid factor. Autoantibodies have been detected in blood samples up to 20 years prior to diagnosing Sjögren's disease (Theander et al., 2015).

The autoantibodies most specific for Sjögren's disease target the Ro52, Ro60, and La48<sup>1</sup> antigens, though the antigens are ubiquitously expressed and autoantibodies specific for these proteins have been detected in other autoimmune diseases (Zampeli et al., 2020). All three of these proteins

<sup>1</sup> These are also called Sjögren's-syndrome-related antigen A/Ro (SSA/Ro) and Sjögren's-syndrome-related antigen B/La (SSB/La).

reside inside cells, making it unclear how autoantibodies access them. The association of anti-Ro52, anti-Ro60, and anti-La48 antibodies in Sjögren's disease and other autoimmune diseases, as well as in driving neonatal lupus manifestations, is still incompletely understood. Given their ubiquitous expression and association with so many different autoimmune manifestations and diseases, it is worth considering further studies to identify the factors contributing to the immune system targeting these antigens and the subsequent effects of the autoantibodies on immune regulation or dysregulation as a potential pathogenic component of the autoimmune disease process.

### Diagnostic Tools

Diagnosing Sjögren's disease is not straightforward given the lack of a single diagnostic test or biomarker and that no well-accepted diagnostic criteria exist. Classification criteria developed for use in identifying people with Sjögren's disease for clinical trials often guide diagnosis, but these criteria were not intended to accurately diagnose all individuals with Sjögren's disease (Vivino et al., 2019).

Diagnostic testing includes measuring the cardinal features of Sjögren's disease: autoantibodies as biomarkers, inflammation of the affected glands on biopsy, salivary gland biopsy, salivary gland function, and lacrimal gland function. Imaging the glands with magnetic resonance imaging (MRI) or ultrasound may also provide supportive information. Ultimately, diagnosis depends on the opinion and experience of the physician, but generally requires a combination of abnormal test results, with either autoantibodies specific for Sjögren's disease or positive lip biopsy required to support a Sjögren's disease diagnosis.

The most reliable biomarker currently available is the anti-SSA/Ro antibody, which comprises two different antibodies targeting Ro52 and Ro60, but anti-SSA/Ro antibodies may be absent in up to 25 to 30 percent of individuals with Sjögren's disease. Some studies have suggested that antinuclear antibodies and rheumatoid factor might also serve as biomarkers, though the utility of each in diagnosing Sjögren's disease is a matter of debate. When these antibodies are absent, the diagnosis becomes more difficult, especially early in disease, such as in childhood, when features of dryness may be absent. The lack of more reliable biomarkers for early diagnosis represents a barrier to diagnosis, as well as a key gap in understanding the disease process.

### Treatments and Prospects for Cures

Current treatments for the glandular manifestations of Sjögren's disease aim to replace tears and saliva or to stimulate increased production

from the individual's own glands, but these approaches do not alter the inflammatory response and are only moderately helpful in relieving dryness. Anti-inflammatory eye drops may help control the damage to the ocular surface, but again, they do not alter the ongoing systemic autoimmune response. No medications have been identified to adequately modulate the autoimmune response or to prevent progression from early stages of disease, such as in children or young adults, to the more profound dryness and associated complications that occur later in disease. Similarly, treatments for the progressive fatigue and musculoskeletal pain are lacking.

When extra-glandular manifestations develop, clinicians may consider immunomodulatory therapies commonly used to treat other autoimmune diseases. There are published consensus guidelines that aim to help direct therapeutic decisions based on manifestations (Lee et al., 2021; Ramos-Casals et al., 2020; Vivino et al., 2016). However, the U.S. Food and Drug Administration (FDA) has not approved any systemic immunomodulatory medications for treating Sjögren's disease, and large clinical trials of potential therapies have generally failed to reach primary endpoints despite promising preliminary data from earlier trials (Fox and Fox, 2016). It is not clear whether these failures are a result of suboptimal selection of individuals with Sjögren's disease or endpoint measures, varied disease mechanisms, or lack of well-established disease activity biomarkers. Given the lack of adequate treatments and incomplete understanding of the pathogenesis of Sjögren's disease, no realistic prospects for cures exist at this time.

### Heterogeneity in Disease

The committee determined that Sjögren's disease is an example of the types of heterogeneity that occur in autoimmune disease. The degree of heterogeneity in many aspects of Sjögren's disease is a barrier to more reliable diagnosis and effective treatments. Studies have found variations in clinical features associated with geolocation, ethnicity, and ancestry (Brito-Zerón et al., 2017; Taylor et al., 2017). One recent study used hierarchical cluster analysis to stratify people with Sjögren's disease into four clusters based on the severity of common symptoms of the condition (pain, fatigue, dryness, anxiety, and depression) and found significant differences among clusters in immunological measures, including autoantibodies, blood lymphocyte counts, and measures of B cell activity (Tarn et al., 2019). Applying this clustering technique to participants of prior clinical trials that failed to demonstrate efficacy did identify treatment effects within specific clusters. This retrospective analysis suggests that

the heterogeneity of features contributed to the lack of efficacy in these failed clinical trials, which considered only the total study population.

From a pathophysiologic perspective, investigators demonstrated the heterogeneity of the interferon signature in the labial minor salivary gland biopsy specimens of individuals with Sjögren's disease (Hall et al., 2015). Specifically, they found a high interferon signature in 58 percent of the individuals, and further analyses demonstrated that among these individuals the interferon signature was dominated by type I interferon in 29.0 percent of the biopsy samples, type II interferon in 35.5 percent of the samples, or a combination of type I and type II interferon in 35.5 percent of the samples. Moreover, several immunological measures, including white blood cell counts, immunoglobulin levels, autoantibodies, degree of salivary gland inflammation, and measures of gland dysfunction, varied between individuals with high or low interferon pathways, and some features also varied based on the type of interferon dominating the interferon signature pattern. These findings suggest that different immunological pathways may drive different clinical and laboratory parameters, contributing to disease heterogeneity.

Along these lines, a recent study of multi-omic profiling of whole blood samples from individuals with Sjögren's disease defined a molecular classification strategy that led to clustering of individuals in four cohorts based on gene expression, genetic risk loci, epigenetics, immunologic analyses—cytokine profiles and flow cytometric-based characterization of immune cells—and clinical data (Soret et al., 2021). This study also found interferon signatures within three of the four clusters that included differing contributions from type I or type II interferons, depending on the cluster. Differences in cytokine and immune cell profiles suggested a greater contribution of acute inflammation in one cluster, which may have therapeutic implications.

Together these studies identify disease heterogeneity in immunological mechanisms, laboratory measures of disease, and clinical features. Better understanding and definition of disease heterogeneity may provide key insight to better direct specific immunomodulatory therapies for different clusters of individuals with Sjögren's disease, a key step toward a personalized medicine approach for this disease.

### Animal Models

Investigators have described and used a variety of animal models to study various aspects of the autoimmune process that occurs in Sjögren's disease (Abughanam et al., 2021). While no one animal model perfectly recapitulates the human disease, several models develop spontaneous autoimmunity with features similar to Sjögren's disease in humans,

including the characteristic lymphocyte-dominant inflammation of lacrimal or salivary glands, autoantibodies, and decreased production of tears and saliva. Several inbred mouse strains or genetically modified mouse strains spontaneously develop Sjögren's disease-like disease, providing a model to study the early immunopathogenic mechanisms that cannot currently be studied in humans because of the lack of predictive biomarkers. Investigators have also used immunization of purified antigenic proteins or viral infection to induce Sjögren's disease-like autoimmunity in other animal models.

### Research Progress and Gaps

Despite the many gaps in understanding Sjögren's disease, investigators have made considerable progress in defining genetic associations (Harris et al., 2016; Imgenberg-Kreuz et al., 2019; Liu et al., 2016), pathologic roles of innate and adaptive immunity (Chivasso et al., 2021), and mechanisms involved in the development of lymphomas in Sjögren's disease (Stergiou et al., 2020). This progress has contributed to an increased awareness of Sjögren's disease and an increase in clinical trials. However, key gaps remain as obstacles to early diagnosis and effective treatments.

One such barrier is the prolonged time between autoimmunity onset and diagnosis, resulting from the lack of highly sensitive diagnostic biomarkers and the lack of awareness of the early manifestations of disease among clinicians. Identifying early diagnostic biomarkers would aid in developing diagnostic criteria aimed specifically at diagnosis in the early stages of disease, or if possible, prior to the development of clinical features. Such predictive biomarkers would promote interventional studies to alter the disease course before the development of end-organ damage that may be difficult to reverse. The molecular characterization of Sjögren's disease has contributed to defining key aspects of disease heterogeneity, but at present the different subtypes and specific mechanisms of Sjögren's disease are not well defined. The prolonged course of autoimmunity leading to diagnosis and the lack of adequate surrogate endpoints make clinical trials less practical, and may be contributing significantly to the failure of clinical trials to meet study endpoints. However, identifying clinical features that would enable better classification of patients with different disease subtypes may enhance the feasibility and effectiveness of clinical trials. As noted above, a better characterization of the life course of individuals with Sjögren's disease is needed.

Sjögren's disease occurs at least as commonly (or more commonly) in individuals with other autoimmune diseases, including rheumatoid arthritis, SLE, and scleroderma, as it does in individuals without other autoimmune diseases, but specific studies aimed at identifying similarities

and differences in clinical features, genetics, immunological features, and disease course are lacking. Epidemiologic studies to define the incidence and prevalence of Sjögren's disease regardless of the presence of co-occurring autoimmune diseases are greatly needed. In some individuals later diagnosed with Sjögren's disease, the initial presentation occurs early, during or after pregnancy in the form of neonatal lupus, which can lead to a range of features in the infant resulting from the passage of autoantibodies characteristic of Sjögren's disease to the fetus during development, as described above. Factors that contribute to the severity of features manifested in the infant are not well-defined, and factors that promote development of neonatal lupus, especially in previously asymptomatic mothers, as an initial manifestation of the presence of Sjögren's disease-associated autoantibodies are poorly understood. Similarly, the specific mechanisms by which these antibodies cause neonatal lupus manifestations, which themselves are heterogeneous among affected individuals, may provide insight into potential pathologic contributions of these autoantibodies to individuals with Sjögren's disease.

## SYSTEMIC LUPUS ERYTHEMATOSUS

SLE, a systemic inflammatory illness, is the prototype systemic autoimmune disease, characterized by multi-organ inflammation (Vaillant et al., 2021). The disease is chronic, extremely heterogeneous in manifestation, and it affects mostly young women and disproportionately those of color. SLE can occur in children, most often during the teen years, and symptoms may be similar to those of adults but more severe (Cleveland Clinic, 2021). A distinctive sign of SLE, a facial rash in the shape of a butterfly that spreads across both cheeks, occurs in many but not all cases (Mayo Clinic, 2021b). Arthritis, rash, cytopenias, lupus nephritis, and neurologic abnormalities are the most common abnormalities signaling the presence of SLE. The disease may be lethal, but most people with SLE suffer unpredictable flares and spontaneous or treatment-induced remissions (Thanou et al., 2021) and suffer damage resulting from active disease and / or its treatment. Most flares, however, have no obvious inciting event.

### Epidemiology and Impact

Information on disparities in the epidemiology of SLE can be found in Box 3-2.

**BOX 3-2**  
**Systemic Lupus Erythematosus (SLE): Sex, Age, Racial and Ethnic Disparities**

- 80-90 percent of affected individuals are women
- U.S. incidence rates for women are 5-10 times higher than for men across all ages and in each racial or ethnic group studied (Dall'Era et al., 2017; Izmirly et al., 2021a; Lim et al., 2014; Somers et al., 2014)
  - Black women have a higher rates of disease than White women, with incidence in Black women rising markedly between ages 20 and 60
- Prevalence per 100,000 women: American Indian and Alaska Native, 270.6; Black, 230.9; Hispanic, 120.7; White 84.7; and Asian and Pacific Islander, 84.4 (Izmirly et al., 2021b)
- Fifth leading cause of death in U.S. Black and Hispanic females ages 15–24 years old (Yen and Singh, 2018)
- Annual incidence in Medicaid-enrolled children ages 3–18: 2.22 per 100,000; 0.72 per 100,000 annual incidence of lupus nephritis (Hiraki et al., 2012)
- Prevalence in Medicaid-enrolled children ages 3–18: 9.73 per 100,000
  - 84 percent female, 40 percent Black, 25 percent Hispanic, and 21 percent White; 3.64 per 100,000 prevalence of lupus nephritis (Hiraki et al., 2012)
- Prevalence and incidence rates of SLE and lupus nephritis increase with age, are higher in girls than in boys, and are higher in all non-White racial and ethnic groups (Hiraki et al., 2012)
- There are disparities in outcomes in children, including care delivery and related conditions such as mental health disorders (Rubinstein and Knight, 2020)
  - Black children and children from southern states have twice the risk of death compared with White children and children from northeastern states (Knight et al., 2014)
- End-stage renal disease (ESRD) resulting from SLE increased from 1995 to 2006 in Black individuals ages 5–39 with lupus nephritis (Costenbader et al., 2011)
  - Black children were half as likely to receive a kidney transplant as White children and twice as likely to die from ESRD caused by lupus nephritis
  - Hispanic children and adults, compared with non-Hispanic children and adults, were less likely to receive kidney transplants
  - Children in the U.S. West and Northwest were placed on kidney transplant wait lists more often than children living in the South (Hiraki et al., 2011)

*Complications, Other Morbidity, and Long-Term Consequences*

SLE affects every organ system; damage accrues through active inflammation, thrombosis, and repair and scarring processes. Individuals with SLE are subject to inflammatory disease such as pericarditis, valvulitis, and myocarditis (Fava and Petri, 2019; Wallace and Gladman, 2019); atherosclerotic disease including micro- or macrovascular myocardial infarction (Roman et al., 2003); stroke caused by vasculitis, thrombosis,

and atherosclerosis (Wallace and Gladman, 2019); and peripheral neuropathy (Fava and Petri, 2019). In addition, persons with the disease may experience renal failure resulting from glomerulonephritis, tubulointerstitial disease, hypertension, and/or vasculitis (Fava and Petri, 2019) as well as a modestly increased risk of lymphoma (Bernatsky et al., 2014). Side effects of treatment include coronary artery disease; retinopathy, including cataracts; osteoporosis; and osteonecrosis, bone death caused by poor blood supply, which can lead to fractures (Fava and Petri, 2019; Gladman et al., 2018; Kamphuis and Silverman, 2010; Wallace and Gladman, 2019). Premature atherosclerosis and bone-related complications, including osteoporosis and osteonecrosis, are important SLE-related complications. Prior to 1955, less than 50 percent of patients survived 5 years after diagnosis; now, 10-year survival exceeds 90 percent. This has resulted in an increased rate of reported musculoskeletal conditions (Kennedy and Khan, 2015).

Some patients may report that osteonecrosis causes a greater reduction in their quality of life than SLE as the underlying systemic disease. Treatment with high dose steroids can lead to osteonecrosis and pain and reduced function can be severe, warranting surgical intervention such as joint replacements. After such surgery, such individuals can be at higher risk for implant infection, discharge to an inpatient facility, more expensive hospital bills, and increased blood transfusions than people without SLE (Singh and Cleveland, 2019).

People with SLE are also highly susceptible to bacterial, fungal, viral, and mycobacterial infections, primarily in the setting of aggressive therapy with corticosteroids and/or small molecule and biologic immunosuppressant agents, but occasionally in association with disease-induced severe leukopenia or lymphopenia (Fava and Petri, 2019). Patients suffer depression, anxiety, and psychosis caused by central nervous system disease, the effects of medications such as corticosteroids, and personal adaptation to living with an unpredictable, disabling, and painful disease (Roberts et al., 2018; Siegel et al., 2021; Zhang et al., 2017).

About 40 percent of people with SLE test positive for antiphospholipid antibodies (aPL) (Garcia and Erkan, 2018; Meroni and Tsokos, 2019). Between 20 and 40 percent of people with SLE have other autoimmune illnesses, such as autoimmune thyroid diseases (Klionsky and Antonelli, 2020) or Sjögren's disease (Wallace and Gladman, 2019), or have features of other autoimmune illnesses such as overlapping thrombocytopenia, Raynaud's syndrome, or rheumatoid arthritis, also known as "rhupus" (Antonini et al., 2020; Jia et al., 2017; Lockshin et al., 2015).

Pregnancies are high risk for some women with SLE, with most complications related to hypertension, renal disease, or antiphospholipid syndrome rather than to active SLE (Sammaritano et al., 2020). Preeclampsia

and premature birth are common complications as well. If the pregnancy is not complicated, children of mothers with SLE who do not have certain autoantibodies are born healthy. However, antiphospholipid antibodies predict preeclampsia and placental dysfunction that leads to fetal growth restriction and/or death. Anti-SSA/Ro and anti-SSB/La occur in all children with neonatal lupus syndrome, which occurs in a minority of children born to women who carry these antibodies (Yoshimi et al., 2012). Neonatal lupus is characterized by hepatitis, cytopenias, and rash, which are transient and common, and congenital heart block, which is permanent but rare (Diaz et al., 2021). Maternal autoantibodies persist in the mothers but not typically in babies beyond the first year of life (Zuppa et al., 2017). Except when the mother is taking contraindicated medications, breastfeeding is safe for both mother and child (Sammaritano et al., 2020).

Phenotypic heterogeneity—the differing presentations of SLE—precludes the ability to confidently predict disease progression. SLE is a lifelong illness, with 10-year survival rates of greater than 90 percent and continuing inflammation and illness- and treatment-related damage driving patient-specific outcomes (Reppe Moe et al., 2021; Singh and Yen, 2018). The illness is more episodic than progressive, with flares and remissions. Damage accrues in different organs at different rates and may vary based on severity of inflammation, differences in healing mechanisms and scarring, and differing effects of medication.

SLE severely affects quality of life in many ways. Most patients suffer fatigue and neurocognitive and musculoskeletal symptoms including pain and weakness (Natalucci et al., 2021; Olesinska and Saletra, 2018; Takase et al., 2021). SLE causes changes in body image as a result of SLE-related effects such as skin rashes and hair loss, and changes in mental status as a result of both the disease and its treatment (Olesinska and Saletra, 2018; Yoon et al., 2019). The disease adversely affects the individual's family relations, personal relationships, physical fitness, and sexual activity (Olesinska and Saletra, 2018). Invisible symptoms may prompt disbelief in family, acquaintances, and even physicians. Coexisting diseases complicate evaluation and treatment of SLE. Recent studies of SLE indicate patients' and physicians' desire to see improved quality of life as a target of treatment (Kernder et al., 2020; Pereira et al., 2020; Shi et al., 2021) by non-pharmacological (Chang et al., 2021) and pharmacological interventions (Jolly et al., 2021).

### *Economic Impact*

The economic costs of SLE are high, comprising both direct costs for delivery of medical care and indirect costs for lost employment productivity (Abu Bakar et al., 2020; Agarwal and Kumar, 2016), as well as

intangible costs resulting from pain and suffering. Studies of direct costs have shown that patients with SLE incur health care costs that are twice as high as a control population. Acute hospitalization accounts for up to 50 percent of these increased costs, followed by medications and physician visits (Panopalis et al., 2012). Higher costs are associated with SLE renal disease, higher disease activity, and impaired physical and mental function. In a large U.S. study of adults with SLE, total unadjusted costs were significantly higher among Medicaid-insured than commercially insured patients (Clarke et al., 2020; Panopalis et al., 2012).

As a significant cause of work disability in the United States, the indirect costs of SLE also convey a high individual and societal cost resulting from unemployment and decreased productivity. A longitudinal study found that 49 percent of adults with SLE in the southeastern United States experienced work loss over an average disease duration of 13 years. Those most affected had severe disease activity and organ damage, and Black residents were more likely than White residents to experience unemployment as a result of having SLE (Drenkard et al., 2014). In addition, for those individuals remaining employed, impaired work productivity was associated with severe fatigue, and neurocognitive and musculoskeletal symptoms.

### Risk Factors and Etiology

The cause of SLE is unknown, though there appears to be a genetic contribution. Family histories of SLE and related autoimmune diseases are common in close relatives of individuals with SLE (Kuo et al., 2015). Twin studies show much higher concordance in identical than in fraternal twins (Block et al., 1975, 1976; Deapen et al., 1992; Reichlin et al., 1992). Many people with SLE have been found to have susceptibility genes that are thought to be contributory but not directly causal in the development of SLE. These include genetic variants in HLA and non-HLA coding regions, some of which have been found to play a role in immune regulation (Ghodke-Puranik and Niewold, 2015). In addition, many people once thought to have early-onset SLE are now known to have specific single-gene (monogenic) mutations, often in interferon pathways. Interferon pathway abnormalities are common. Examples are VEXAS syndrome and Aicardi-Goutière syndrome (Beck et al., 2020; Demirkaya et al., 2020). No consensus exists on whether monogenic SLE-like illnesses should be classified as a subset of SLE or as separate genetic disorders.

Other than family history, there is limited information on risk factors or etiologies for initiation of SLE, though exogenous events such as infection or extensive ultra-violet light exposure may trigger exacerbations of SLE, including the first symptoms that bring an individual to medical care

(Estadt et al., 2021; Harley and James, 2006). Environmental exposures that have most consistently been associated with risk of developing SLE are occupational exposure to respirable silica (Morotti et al., 2021), smoking history (Parisis et al., 2019), and vitamin D deficiency (Hassanalilou et al., 2017; Young et al., 2017). Viral infections and microbiomic factors may play a role in inducing or exacerbating SLE in susceptible persons (Quaglia et al., 2021). A recent meta-analysis of 33 studies found a significantly higher seropositivity for EBV antibodies in persons with SLE compared with controls (Li et al., 2019). Recent studies have also found associations between psychosocial trauma and depression with increased risk for developing SLE (Bookwalter et al., 2020; Roberts et al., 2017, 2020). The above environmental and psychosocial factors may contribute to epigenetic changes that modify expression of SLE-related genes, thereby leading to immune dysregulation (Ghodke-Puranik and Niewold, 2015).

### Diagnostic Tools

The heterogeneous phenotypes, laboratory manifestations, and prognoses of SLE make diagnosis challenging. Disease severity for SLE ranges from trivial to lethal, and clinical presentations most often include arthritis, skin rashes, kidney disease, and blood disorders, though SLE can affect every organ in the body in any order at any time. SLE may present as an acute illness or it may take decades after first recognition of symptoms or abnormal laboratory tests to become clinically diagnosable (Arbuckle et al., 2003). Patients with nephritis only, rash only, or hematological manifestations only—and sharing no other clinical features—can all be said to have SLE. Some patients present with specific manifestations, such as seizure or renal failure, while others first develop a symptomatic problem a decade or more after first being diagnosed. Though trigger factors that induce flares, such as infection, sunlight exposure, allergic reactions, may play a role in a few individual patients, the timing of manifestations in most patients is not understood.

Autoantibodies are the most consistent laboratory feature of SLE. Most people with the condition have high titer antinuclear antibody, but antinuclear antibody is commonly found in other autoimmune diseases, such as Hashimoto's thyroiditis, Sjögren's disease, and scleroderma, as well as in otherwise normal people on occasion (Wallace and Gladman, 2019). Anti-DNA antibody and anti-Smith antibody, when present at high titer in symptomatic individuals, are diagnostic of SLE. In asymptomatic individuals, these autoantibodies suggest but do not predict future clinically evident SLE (Wallace and Gladman, 2019). Other autoantibodies, including anti-ribonuclear protein, anti-SSA/Ro, and anti-SSB/La are

commonly seen in people with SLE but are not diagnostic and instead may suggest concomitant Sjögren's disease or mixed connective tissue disease (Pisetsky, 2020). Individuals with SLE usually have abnormal markers of inflammation, including erythrocyte sedimentation rate, C-reactive protein, and complement activation, and about half of those with SLE have proteinuria. When clinically indicated, skin, kidney, and other biopsies provide definitive diagnostic information (Wallace and Gladman, 2019).

Investigators have developed classification criteria for SLE for research purposes as a potential means of identifying relatively homogeneous groups of patients for inclusion in studies and trials. In 1982 and again in 1997, the American College of Rheumatology (ACR) published SLE classification criteria (Hochberg, 1997; Tan et al., 1982). The 2012 Systemic Lupus International Collaborating Clinics classification criteria (Petri et al., 2012) updated the ACR criteria to refine the SLE definition, include additional clinical and lab criteria, and emphasize SLE as primarily an autoantibody driven disease. These criteria are not limited to research purposes (Fava and Petri, 2019). Most recently, the 2019 European Alliance of Associations for Rheumatology<sup>2</sup> and ACR Rheumatology revised SLE classification criteria for research (Aringer et al., 2019; Fava and Petri, 2019), now requiring antinuclear antibody as an entry criterion for clinical trials, along with a weighted and additive scoring system for other criteria. While these classification schema are useful for clinical guidance, being specific but not sensitive, they are most appropriate for use in research rather than clinical diagnosis and management.

### Treatments and Prospects for Cures

Most clinical and basic research studies of SLE involve patients who fulfill classification criteria, excluding almost half of patients who are considered by their physicians to have SLE but who do not fulfill these criteria (Jia et al., 2017; Lockshin et al., 2015, 2019). Specific severity, organ system involvement, and duration-related details dictate treatment, the latter focusing on accrued damage from either illness or its treatment. A number of entities have developed general treatment guidance. Some treatment recommendations, mostly based on systematic literature review, are provided by national and international rheumatology societies such as the ACR and the European Alliance of Associations for Rheumatology (Fanouriakis et al., 2019). Other recommendations are expert opinions that are not necessarily sponsored by organizations (Durcan et al., 2019). More specific treatment protocols exist for subsets of people with SLE, such as those with International Society of Nephrology/Renal Pathology Society

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<sup>2</sup>Formerly the European League Against Rheumatism.

(ISN/RPS) class IV lupus nephritis. Periodic treatment changes are common. Approximately one-third of SLE patients discontinue hydroxychloroquine—a first line of treatment—because they experience remission or find the medications ineffective (Mehat et al., 2017).

Standard therapies include hydroxychloroquine (the toxicity of which is related to lifetime dose), topical and systemic corticosteroids, and small molecule immunosuppressants such as mycophenolate mofetil, azathioprine, and cyclophosphamide (Durcan et al., 2019; Fava and Petri, 2019). In 2011, FDA approved belimumab, a B cell-depleting agent that has a shorter duration and less-toxic effect than rituximab, for SLE treatment in adults—the first drug approved for SLE in over 50 years. Indications were expanded to include pediatric patients in 2019 and SLE nephritis in 2020. FDA also approved voclosporin, an oral calcineurin inhibitor, in 2021 for the treatment of lupus nephritis, a manifestation of SLE in adults (FDA, 2021a; Rovin et al., 2021). Cytokine inhibitors targeted to type 1 interferon, such as anifrolumab, reduce disease activity (Morand et al., 2020). Anifrolumab was approved for use in SLE in 2021 (FDA, 2021c).

Because uncontrolled immune response, usually expressed by autoantibodies, is the likely cause of SLE symptoms, studies are focusing on monoclonal antibodies to block specific cellular and molecular pathways thought to be abnormal in SLE. Targets of therapies in ongoing clinical trials include B cells that synthesize autoantibodies (dapirolizumab, obinutuzumab) and T cells that instruct B cells as to what antibodies they should produce (itolizumab, ALPN-101). The interferon pathway is another clinical trial target (BIIB059). Other clinical trials are examining small molecule pharmaceuticals that block binding of antigen to cells (sirolimus) or mark immune and inflammatory cells for destruction (KPG-818) and IL-18 blockers for example.

Morbidity and mortality can result from kidney failure, heart failure, stroke, or infection during immunosuppressive therapy (Murimi-Worstell et al., 2020; Wallace and Gladman, 2019). Additional causes of disability include destructive arthritis, osteonecrosis, osteoporosis, and dementia (Lin et al., 2016; Wallace and Gladman, 2019). There is no known approach for preventing SLE, but long-term studies may be able identify trigger factors for transition from autoantibody-positive but asymptomatic disease to symptomatic disease or triggers for flares in clinically quiescent patients.

### Animal Models

Animal models for SLE have existed for more than four decades (Richard and Gilkeson, 2018). While illustrative of specific mechanisms of illness, such as glomerulonephritis, none can completely reproduce

human SLE. Existing mouse models differ from human SLE in predictability of onset, sex distribution, absence of flares, and remissions, and they are limited for the most part to modeling specific manifestations such as nephritis, dermatitis, or arthritis (Moore et al., 2021; Richard and Gilkeson, 2018). These models do provide hypothesis-testing opportunities when assessing whether specific immune pathways are involved in the disease, and they can find use in testing new potential therapies in early preclinical studies.

### Research Progress and Gaps

Major research progress in SLE consists of understanding—and targeting treatment to—molecular mechanisms that contribute to specific, if limited, forms of the illness (Barrat et al., 2019; Chen et al., 2021). Progress in understanding SLE will require research that leads to a better understanding of the basis of heterogeneity, change over time, epidemiology, and the relationship between phenotypic heterogeneity and disease progression. For instance, despite extensive genetic, epigenetic, and environmental data, questions remain as to why SLE affects mostly women, more non-White people, and mostly young persons; why SLE flares and remits; and why in some people SLE targets the kidneys, and in others the skin, joints, or blood (Lockshin, 2007). Research to identify the circumstances that trigger transition from autoantibody-positive to clinical SLE, or the triggers for flares in clinically quiescent people with the disease could lead to prevention and early intervention or treatment. In areas such as neuropsychiatric SLE (NPSLE) advances in biomarkers and disease models are needed. There is an unmet need for diagnostic biomarkers and innovation in imaging modalities for NPSLE (Kivity et al., 2015). Although some autoantibodies have been suggested as a potential biomarker, only a few antibodies have met the exploratory criteria and are being used in the diagnosis and therapeutic decisions (Govoni and Hanly, 2020; Sarwar et al., 2021). In addition to biomarkers, attention to models is also critical as in the case of neuropsychiatric manifestations of SLE (Karnopp et al., 2021).

Additionally, more research is needed to identify risk factors, including environmental and psychosocial factors that contribute to disease initiation. Over the past few years, however, investigators have made advances in understanding the pathophysiologic mechanisms underlying the heterogeneity of SLE, guiding drug development and leading to some successful clinical trials and FDA drug approval as noted above. Gaining a better understanding of the mechanisms triggering onset of SLE and those contributing to disease activity over time requires conducting additional longitudinal studies, collecting epidemiologic data, and using

life-course methodologies. In the interim, developing more sensitive classification schema for clinical diagnosis and disease management could improve the care of persons who may have SLE but who, under current guidelines, do not receive a diagnosis or treatment for the disease.

## ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS), which was initially thought to be a subset of SLE but was defined as a separate syndrome in 1989 (Lockshin and Harris, 2017), has three manifestations. Thrombotic APS occurs in episodes, often triggered by an infection or a change in therapy, and is characterized by recurrent thromboses, heart valve disease, and a type of microangiopathic kidney involvement that differs from that seen with SLE. Long-term outcomes for thrombotic APS depend on the extent and location of thromboses; for example, one case could lead to deep vein thrombosis and another to stroke.

Obstetric APS is characterized by recurrent pregnancy complications including fetal growth restriction, fetal death, and severe preeclampsia. Most women with obstetric APS do not have thrombotic APS, and women with thrombotic APS do not necessarily develop obstetric APS (Garcia and Erkan, 2018; Simioni, 2012). However, women with APS who have suffered preeclampsia are at increased risk for cardiovascular events later in life (Simard et al., 2021).

Catastrophic APS (CAPS), a highly lethal form of the disease, affects less than 1 percent of those with APS (Cervera, 2017; Cervera and Group, 2010). In CAPS, severe, often lethal multi-organ thromboses occur over short periods of time (Garcia and Erkan, 2018).

### Epidemiology and Impact

Information on disparities in the epidemiology of APS can be found in Box 3-3.

#### BOX 3-3 Antiphospholipid Syndrome (APS): Sex, Age, Racial and Ethnic Disparities

- The female-to-male ratio for APS is 1.0 for individuals ages 18 and older
- APS associated with SLE is female predominant
- The risk of APS is greatest in White populations and relatively low in Black populations (Garcia and Erkan, 2018)

### *Complications, Other Morbidity, and Long-Term Consequences*

Coexisting disease, overlap syndromes, progressive damage, and the adverse effects of treatment complicate APS. For example, in one small study, 33 percent of patients with APS had concomitant autoimmune disease, and over half of those had concomitant SLE (Abu-Zeinah et al., 2019). Women with obstetrical APS may have increased risk of hypertension and renal failure (Garcia and Erkan, 2018), and individuals with thrombotic APS suffer long-term disabilities resulting from neurologic, cardiac, and renal injury. The presence of SLE, history of arterial thrombosis, and organ damage can adversely affect health-related quality of life for individuals with APS (Desnoyers et al., 2020). Pain, fatigue, concerns about family planning, and medication unpredictability can also take a toll on the mental health of individuals with APS (Chighizola et al., 2021; Desnoyers et al., 2020). Death can result from kidney, brain, or cardiopulmonary thromboses, including heart valve disease and thrombotic microangiopathy occurring either separately or concomitantly, as in CAPS.

### *Economic Impact*

Data on the economic impact of APS are lacking. Direct costs of care delivery include frequent physician visits, emergency room visits, hospitalizations, anticoagulant medication, and laboratory costs for close medication monitoring. Studies have found that impaired work productivity adds to the indirect costs of APS (Chighizola et al., 2021). However, quantitative data for the direct and indirect costs of APS are not available.

### **Risk Factors and Etiology**

Other than family history, research has not identified risk factors for APS. The frequent observation (Garcia and Erkan, 2018) that infections trigger transient antiphospholipid antibodies points to an environmental cause, perhaps characterized by an abnormal response to exposure. Many infections, including syphilis, leprosy, and COVID-19, induce antiphospholipid antibodies transiently, though it is not yet clear whether infection-induced antibodies are pathogenic (Asherson and Cervera, 2003b; Ribeiro et al., 2019; Talotta and Robertson, 2021). Antiphospholipid antibodies persist over long periods of time.

Research suggests a genetic susceptibility for APS but has yet to define what that susceptibility might be (Gavriş et al., 2021; Lopez-Pedrera et al., 2019). Immobility, infection, smoking, and withdrawal of anticoagulant medication each can trigger thrombotic episodes (Cundiff, 2008; Johns Hopkins Medicine, n.d.), and microbiomic or other environmental factors may trigger APS in susceptible persons (Martirosyan et al., 2019; Ruff et

al., 2019). Antiphospholipid antibody, specifically lupus inhibitor, and pre-existing renal dysfunction predispose women to obstetric complications. Between thrombotic or obstetric episodes, people with APS do not have abnormal markers of inflammation and are mostly asymptomatic, though a small proportion of those with APS have ongoing cutaneous vasculitis or thrombocytopenia. Withdrawal of therapeutic anticoagulation, infection, and trauma can trigger CAPS.

### Diagnostic Tools

By definition, people with APS must have persistent moderate-to-high titer immunoglobulin G (IgG) and/or immunoglobulin M (IgM) anticardiolipin, anti-beta-2-glycoprotein I, or lupus inhibitor antibodies, primarily of IgG isotype. These antibodies are sensitive for APS but not specific; many individuals with these antibodies are healthy or have alternate explanations for their presence (Gkrouzman et al., 2021; Misasi et al., 2015).

A classification criteria diagnosis of APS requires both a compatible clinical event such as pregnancy loss or thrombosis, and because infection-induced antibodies are usually transient, persistent high-titer anticardiolipin, anti-beta-2-glycoprotein I, or lupus inhibitor antibodies. Research has found other related autoantibodies that have not yet received official endorsement as biomarkers for APS, primarily because worldwide standards are not yet available. Individuals who do not meet criteria can nonetheless receive an APS diagnosis if they show atypical features, such as livedo racemosa, microvascular thrombosis, or Libman-Sacks endocarditis, together with positive serology. People who are acutely ill, specifically those with CAPS, can be diagnosed and treated without demonstrating that antibodies are persistent.

In patients with APS, a positive lupus inhibitor test has a high predictive value for pregnancy loss (Yelnik et al., 2016), and a global anti-phospholipid syndrome score (GAPSS) has a high predictive value for thrombosis (Zuily et al., 2015).

### Treatments and Prospects for Cures

Treatments for APS are based more on expert consensus than on clinical trial data and include aspirin, hydroxychloroquine, heparin and warfarin for acute thromboses, and heparin for pregnancies in women with prior pregnancy complications (Garcia and Erkan, 2018). Since most women with obstetric APS do not develop future thromboses, anticoagulation can be discontinued a few months postpartum. Treatment for thrombotic APS is usually lifelong anticoagulation with warfarin.

Hydroxychloroquine may improve outcomes in both thrombotic and obstetric APS (Garcia and Erkan, 2018; Sciascia et al., 2016). Although hydroxychloroquine may reduce the risk of thrombosis in patients with SLE, its efficacy is not yet proven for patients with APS who do not have SLE (Garcia and Erkan, 2018). Based on small prospective studies, individuals with atypical features such as leg ulcers, endocarditis, or neurologic or renal disease may benefit from use of rituximab (Garcia and Erkan, 2018). Researchers are also investigating anticomplement therapies such as eculizumab and endothelial protective therapy with statins (Garcia and Erkan, 2018). Antiphospholipid antibodies disappear over years in some people with APS, suggesting the possibility of withdrawal of anticoagulation for some patients. Research suggests that direct oral anticoagulants may be useful in the treatment of some mild and/or atypical APS patients, that is, those without thromboses or pregnancy losses. Direct oral anticoagulants are not recommended for higher risk APS patients, that is, patients who are pregnant; have histories of arterial or small vessel thromboses; or have triple positive antiphospholipid antibodies (lupus anticoagulant, aCL, and anti- $\beta$ 2GPI antibodies) (Dufrost et al., 2020).

### Animal Models

No spontaneous animal models of APS exist. Passively acquired antiphospholipid antibodies cause pregnancy loss and induce thrombosis; similarly *in vitro* studies on platelets, endothelial cells, and leukocytes suggest that autoimmune antiphospholipid antibodies are not secondary events but are directly pathogenic (Gandhi et al., 2021). There is no available infection-induced animal model of APS (Asherson and Cervera, 2003a; Garcia and Erkan, 2018). Discovery of such models would improve understanding of APS mechanisms.

### Research Progress and Gaps

Epidemiologic data for APS are unavailable. Research has not identified the circumstances that trigger transition from autoantibody negative to positive or antibody positive to clinical APS, nor has it identified the triggers for flares in people who are clinically quiescent. Research gaps include the sources of the autoantibodies, evidence that the currently demonstrated autoantibodies are the primary actors, triggers for events, and the mechanisms by which the illnesses progresses. The interrelationship of APS with conditions such as NPSLE poses an additional level of complexity and challenges for research. Recent advances in epidemiology, genetics, and cell and cytokine biology promise progress in this area. Endothelial injury is a new area of exploration, especially since there

seem to be clear links between COVID-19 infection and the inflammatory and immunological injury seen in SLE and APS (Vlachoyiannopoulos et al., 2020; Winchester et al., 2021). Proposed treatment paradigms need confirmation with controlled clinical trials, and long-term prognosis data are needed. An international voluntary consortium (APS ACTION) is assembling worldwide data from clinics specializing in APS (Erkan et al., 2021). Additionally, quantitative data for the direct and indirect costs of APS are needed to determine the economic impact of the disease.

## RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a complex chronic disease characterized by joint inflammation, pain, swelling, and damage as well as by a variety of effects seen in the skin, lung and cardiovascular systems. Other generalized symptoms include fatigue and weight loss. Like many other autoimmune diseases, rheumatoid arthritis is characterized by periods of flares and remission, with long-term consequences including the systemic effects of the disease as well as complications from long-term drug therapies.

### Epidemiology and Impact

Information on disparities in the epidemiology of rheumatoid arthritis can be found in Box 3-4.

**BOX 3-4**  
**Rheumatoid Arthritis: Sex, Age, Racial and Ethnic Disparities**

- The incidence of rheumatoid arthritis begins to rise in women and men ages 35–54, with the highest rates in both women and men among those ages 65–74 (Myasoedova et al., 2010)
- Female-to-male incidence ratios are about 3:1 during reproductive and perimenopausal years and decrease to about 1.5:1 for individuals over the age of 55 (Myasoedova et al., 2010)
- Incidence is higher in the U.S. and Northern European populations (Alamanos et al., 2006)
- Prevalence rates are higher in specific American Indian and Alaska Native communities (Blackfeet, Yakima, Chippewa, and Pima) than in non-Indigenous populations (McDougall et al., 2017) compared to the general U.S. population estimates (Kawatkar et al., 2019)
- Higher disease activity and lower rates of remission occur among Black and Hispanic compared with White populations (Barton et al., 2011; Greenberg et al., 2013)

*Complications, Other Morbidity, and Long-Term Consequences*

Complications and other conditions associated with rheumatoid arthritis stem in large part from the role that chronic inflammation plays in this disease. Chronic inflammation increases the risk of developing atherosclerosis, leading to strokes and myocardial infarction, and the risk of developing pulmonary fibrosis and interstitial lung disease (Kim and Suh, 2020; Lindhardsen et al., 2011). The chronic inflammation associated with rheumatoid arthritis can also damage the skin and eyes (Chua-Aguilera et al., 2017; Murray and Rauz, 2016). An increased risk of different types of lymphoma (Anderson et al., 2009) and of central or peripheral neurological system damage (Kaeley et al., 2019; Ramos-Remus et al., 2012) are also seen in people with rheumatoid arthritis. The results can be broad ranged. For example, significant morbidity, and in some cases, reduced life span, have been associated with central and peripheral neurological damage. Such damage may produce symptoms ranging from numbness in the hand to muscle weakness in all four limbs (quadriplegia) as well as sudden death (Ramos-Remus et al., 2012).

Mortality resulting from cardiovascular and respiratory disease contribute to the increased overall mortality risk in people with rheumatoid arthritis (England et al., 2016; Yoshida et al., 2021). Studies have also found an increased risk of other autoimmune diseases, specifically type 1 diabetes, IBD, and thyroiditis, in people with rheumatoid arthritis, as well as an inverse association between rheumatoid arthritis and multiple

sclerosis (Somers et al., 2009). In addition, an individual may have a form of disease that shares features of both rheumatoid arthritis and SLE, also known as “rhupus”(Antonini et al., 2020; Jia et al., 2017; Lockshin et al., 2015), or one that shares features with Sjögren’s disease (Zhang et al., 2020). The long-term use of immune-suppressing medications increases the risk of infections (Kim and Suh, 2020).

The impact of rheumatoid arthritis on quality of life can be significant. For example, depression is common and is a key component that disease management should address (Matcham et al., 2013).

### *Economic Impact*

The economic impact of rheumatoid arthritis is significant. One comprehensive analysis estimated a total cost of \$47.6 billion (in 2005 dollars), based on estimates of direct health care costs (\$8.4 billion), indirect costs of lost wages productivity, job turnover, and required household help (\$19.3 billion), intangible costs relating to quality-of-life changes (\$10.3 billion), and premature mortality (\$9.6 billion) (Birnbaum et al., 2010).

The measurement of indirect costs is important given a decreasing trend in inpatient costs; this was due to improvement of clinical outcomes by biologic and targeted synthetic disease-modifying antirheumatic drugs. A decreasing trend in inpatient costs chronologically suggested a cost shift in other components of direct costs. Indirect costs still contributed a considerable proportion of total costs, with work disability being the main cost component. Economic analyses that do not incorporate or appropriately measure indirect costs will underestimate the full economic impact of rheumatoid arthritis (Hsieh et al., 2020).

A retrospective study of employed individuals (18–65) using 1996–2006 US Medical Expenditure Panel Survey data estimated national indirect costs of rheumatoid arthritis-related absenteeism as \$252 million annually. The study concluded that there is a higher probability that individuals with rheumatoid arthritis will miss work and workdays than those without rheumatoid arthritis (Gunnarsson et al., 2015).

### **Risk Factors and Etiology**

The autoantibodies seen most commonly in people with rheumatoid arthritis are rheumatoid factor and anti-citrullinated protein/peptide antibodies (van Delft and Huizinga, 2020). In synovial fluid, these autoantibodies may contribute to activation of the inflammatory immune response and the resulting tissue damage.

One of the most well-established risk factors for rheumatoid arthritis is cigarette smoking (Liu et al., 2019). This elevated risk, seen most

strongly and consistently in people with anti-citrullinated protein/peptide antibodies, exhibits a positive dose–response with duration and amount smoked in pack-years. Smoking cessation can delay or prevent development of rheumatoid arthritis. Studies have elucidated the interaction between smoking and the HLA-DR shared haplotype specific gene and the mechanisms through which smoking-mediated immune responses in the lung lead to autoantibody formation and immune activation, and ultimately damage and destruction of joints and other tissues (Stolt et al., 2010). This research has produced important insights into the systemic effects that can be produced by the immune responses to respiratory exposures in the lung (Catrina et al., 2014).

Research has also identified similar mechanisms with other respirable exposures, including silica and asbestos (Klareskog et al., 2020). Investigators have examined occupational silica exposure in numerous studies and found a strong and robust association and evidence of dose–response with various measures of increasing exposure. A 2020 meta-analysis of data from 15 studies found that the overall odds ratio for occupational silica exposure and risk of rheumatoid arthritis was 2.59 (Mehri et al., 2020). This analysis did not include the most recent study (Boudigaard et al., 2021) or several early studies (Brown et al., 1997; Rosenman et al., 1999), each of which provide additional support for the overall strength of the evidence. Silica induces apoptosis of macrophages, exposing intracellular self-antigens to a dysregulated immune response that involves increased production of proinflammatory cytokines, B-cell activation, and increased production of autoantibodies (Cooper et al., 2008).

Multiple studies have examined three risk factors—breastfeeding, alcohol consumption, and obesity—and yielded relatively robust and consistent findings. Breastfeeding appears to be a protective factor, as there is an inverse, dose-dependent association between women who have breastfed and rheumatoid arthritis, with a greater protective effect seen with a longer length of lactation (Chen et al., 2015). In a meta-analysis of six studies, the combined odds ratio was 0.68 for ever breastfeeding, 0.78 for 1 to 12 months of breastfeeding, and 0.58 for more than 12 months of breastfeeding versus never breastfeeding (Chen et al., 2015). Alcohol consumption and rheumatoid arthritis also shows an inverse association, with dose–response following a U-shaped curve (Maxwell et al., 2010; Scott et al., 2013). Higher body mass index is associated with an increasing risk of rheumatoid arthritis, with an estimated odds ratio of 1.15 and 1.31 for the overweight and obese categories, respectively (Qin et al., 2015).

Proinflammatory dietary factors, such as red meat and sugar-sweetened beverages, are associated with increased risk of rheumatoid arthritis, whereas anti-inflammatory diets, fish, and omega-3 fatty acid supplements

are associated with decreased risk of rheumatoid arthritis autoimmunity and rheumatoid arthritis, although not consistently (Benito-Garcia et al., 2007; Di Giuseppe et al., 2014a,b; Gan et al., 2016; Hu et al., 2014, 2017; Pattison et al., 2004; Sparks et al., 2019a,b).

The findings from studies of oral contraceptive use are mixed (Qi et al., 2014). Studies of infectious agents are few in number, but work examining *Porphyromonas gingivalis*, a bacteria associated with periodontitis, provides insights into possible mechanisms relating to production of anti-citrullinated protein/peptide antibodies (Klareskog et al., 2020). EBV has also been associated with development of rheumatoid arthritis. Persons with rheumatoid arthritis have high titers of EBV antibodies and high levels of EBV-infected B cells, which indicate the control of EBV infection is impeded (Balandraud and Roudier, 2018).

Studies examining the development of autoantibodies prior to development of symptomatic disease have advanced the understanding of the etiology of rheumatoid arthritis. Research conducted over the past 20 years has included multiple isotypes of rheumatoid factor and anti-citrullinated protein/peptide antibodies (Deane and Holers, 2021). Using blood banks and other sources of stored sera, retrospective and prospective studies have demonstrated the presence of these autoantibodies five or more years before clinical presentation of disease (Nielen et al., 2004). The highest positive predictive values occur with the presence of two or more autoantibodies (Deane and Holers, 2021). These observations provide the opportunity to develop strategies to prevent the progression from a preclinical to symptomatic disease. At a population level, reducing occupational exposure to respirable silica and discouraging smoking are two steps that could reduce the incidence of rheumatoid arthritis. Additional research is needed to determine whether the permissible exposure limits designed to reduce the risk of silicosis will also provide protection for rheumatoid arthritis and other systemic autoimmune diseases.

### Diagnostic Tools

Many symptoms of early rheumatoid arthritis, such as fatigue and low-grade fever, are nonspecific. The presence of swelling and stiffness in multiple joints is characteristic of the disease, and testing for rheumatoid factor, anti-citrullinated protein/peptide antibodies, and measures of inflammation, including C-reactive protein and erythrocyte sedimentation rate, are a cornerstone of classification criteria (Aletaha et al., 2010).

### Treatments and Prospects for Cures

Maximizing the length of remission periods and decreasing therapy side effects and complications, rather than achieving a cure, are the basis for therapeutic advances. Treatment of rheumatoid arthritis is aimed at reducing symptoms, improving function and quality of life, and preventing progression and damage to the affected areas and other long-term complications. Individuals with rheumatoid arthritis can reduce their medications when they achieve sustained improvements in disease activity. Treatment options include general nonsteroidal anti-inflammatory drugs, and immune-suppressant disease-modifying anti-rheumatic drugs. The latter group includes conventional or traditional agents such as methotrexate and leflunomide, biologics such as tumor necrosis factor (TNF) inhibitors and rituximab, and Janus kinase inhibitors targeted at specific immune pathways. Multiple organizations, including the ACR and the European Alliance of Associations for Rheumatology, have established and updated treatment guidelines (Crofford, 2013; Fraenkel et al., 2021; Singh et al., 2016; Smolen et al., 2020).

### Animal Models

Researchers have developed numerous animal models, primarily in mice and rats, that demonstrate rheumatoid arthritis features including synovial hyperplasia, cartilage damage, bone erosion, and increased production of key proinflammatory cytokines involved in this disease, such as TNF $\alpha$ , interferons, and several interleukins (Choudhary et al., 2018). Researchers developing one of the earliest models in the 1940s used complete Freund's adjuvant, a mixture of mineral oils, heat-killed mycobacteria, and emulsifying agent. Collagen is another common inducing agent, either with complete or incomplete Freund's adjuvant, which omits mycobacterium. The choice of inducing agent, adjuvant, strain, and species enables investigators to examine different mechanisms, stages, and features of the disease. Mice expressing the human TNF gene (Keffer et al., 1991), and more recently, transgenic and knockout mouse models such as K/BxN mice (Monach et al., 2008) enable examination of the role of specific genes in inflammatory response.

### Research Progress and Gaps

Important developments in rheumatoid arthritis over the past 30 years include understanding the heterogeneity of the disease and the usefulness of developing classification criteria to reflect the variability in phenotypes and biomarkers. In addition, researchers have made

considerable progress in developing a wider variety of treatment options based on specific immune pathways, coexisting illness, and individual patient preferences.

Questions pertaining to the development of the disease offer opportunities for research that could lead to prevention and earlier interventions. Studies examining the transition from an asymptomatic preclinical state in which rheumatoid arthritis-specific autoantibodies are present to symptomatic disease are needed. These studies would enable investigation of various environmental factors, and gene–environment interactions, associated with the development of subsets of disease defined by serology. It is also important to understand the role of these factors and interactions in disease progression and development of flares. The role of respiratory exposures and links between immune response in the lung to inflammation and pathology induced in other tissues is another promising avenue of research. Epidemiologically, the signal of recent temporal increases in incidence after years of apparent declines stresses the importance of elucidating environmental and modifiable risk factors and the need for continued public health surveillance for rheumatoid arthritis.

## PSORIASIS

Psoriasis is an immune-mediated systemic inflammatory disease that manifests as chronic inflammatory effects in skin and joints (Reich, 2012). Psoriasis can affect any area of the skin but most typically affects the extensor surfaces of the forearms and shins, the peri-anal, peri-umbilical and retro-auricular regions, and the scalp (Boehncke and Schön, 2015), with up to 80 percent of people having scalp involvement (Ortonne et al., 2009). Multiple variants of psoriasis exist, including plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. Chronic plaque psoriasis, also known as psoriasis vulgaris, accounts for 90 percent of psoriasis cases. Lesions are typified by sharply demarcated erythematous plaques that are covered by plates, or lamella, of silvery scales. The plaques can be few in number or can extend across large areas of the body. Erythroderma is a severe form of psoriasis that covers the entire body and can be life-threatening as a result of electrolyte disturbances and shedding of the outer layer of skin, known as desquamation, that can occur (Armstrong and Read, 2020; Boehncke and Schön, 2015).

### Epidemiology and Impact

Information on disparities in the epidemiology of psoriasis disease can be found in Box 3-5.

**BOX 3-5**  
**Psoriasis: Sex, Age, Racial, and Ethnic Disparities**

- Men and women have a similar incidence, but men may experience more severe disease (Hägg et al., 2013)
- White individuals had the highest prevalence of psoriasis at 3.6 percent, followed by other racial/ethnic groups (including multiracial) at 3.1 percent
  - Hispanic and Black individuals had a lower prevalence of psoriasis (Armstrong et al., 2021)
- Prevalence in U.S. children and adolescence estimated to be 128 per 100,000 person
  - increases with age, from 0.12 percent at age 1 to 1.2 percent at age 18 (Augustin et al., 2010)
  - Prevalence in females is higher in females than males: 146 per 100,000 vs. 110 per 100,000 (Paller et al., 2018)
  - Prevalence in females increases from 30 per 100,000 0- to 3-year-olds to 205 per 100,000 12- to 17-year-olds (Paller et al., 2018)
- Location of lesions and type of psoriasis can vary by age
  - More likely to affect the face in children
  - Guttate psoriasis, which manifests as red, scaly, small, teardrop-shaped spots, is more common among children than adults (Boehncke and Schön, 2015)

*Complications, Other Morbidity, and Long-Term Consequences*

Psoriatic arthritis is a common co-occurring autoimmune disease with psoriasis. An estimated 5 to 40 percent of those with psoriasis develop psoriatic arthritis—characterized by stiffness, pain, and swelling of joints that can eventually lead to debilitating joint destruction—at some point in their lives (Henes et al., 2014; Mease and Goffe, 2005). Psoriasis either precedes or occurs at the same time as psoriatic arthritis in 85 percent of those with psoriasis (Armstrong and Read, 2020).

People with psoriasis, particularly its severe forms, have increased risk of developing cardiometabolic health conditions including type 2 diabetes, metabolic syndrome, coronary artery disease, and stroke (Armstrong et al., 2015; Armstrong and Read, 2020). Likely owing to sharing genetic susceptibility loci on chromosome 16q with Crohn's disease, people with psoriasis have a four times greater prevalence of autoimmune IBD, including Crohn's disease and ulcerative colitis, than the general population (Eppinga et al., 2017; Karason et al., 2003).

Several studies have documented linkages between psoriasis and depression, anxiety, and suicidal ideation (Dalgard et al., 2015; Dowlatshahi et al., 2014; Singh et al., 2017). Psoriasis has a significant physical

and psychological effect, similar to that of other skin lesions, and with a comparable effect on quality of life as hypertension, type 2 diabetes, or depression (Rapp et al., 1999). People with psoriasis may experience pain, itchy skin, and bleeding, and may experience stigma from others (Kimball et al., 2005).

### *Economic Impact*

A 2015 study estimated the total cost of psoriasis in the United States to be \$35.2 billion, with 35 percent, 34 percent, and 32 percent of the costs attributed to direct health care costs, reduced health-related quality of life, and decreased work-related productivity losses, respectively (Vanderpuye-Orgle et al., 2015).

### **Risk Factors and Etiology**

Dysregulated interactions between innate and adaptive components of the immune system with cutaneous cells cause the skin lesions characteristic of psoriasis (Boehncke and Schön, 2015), though little is known about antibodies or antigens involved in the disease. Genetic, environmental, and behavioral factors have been implicated in the etiology of psoriasis, with genetic factors having the largest contribution to psoriasis development (Griffiths et al., 2021; Tsoi et al., 2017). In fact, research in the early 1970s first identified a higher incidence of psoriasis in first- and second-degree relatives of individuals who develop psoriasis compared with the general public. In addition, identical twins are up to three times more likely to share a diagnosis of psoriasis than fraternal twins (Alshabani et al., 2010; Farber and Nall, 1974).

Numerous studies have identified multiple genes and chromosomal regions that increase the risk of developing psoriasis (Tilikainen et al., 1980; Tsoi et al., 2017). Research also suggests that genetic factors influence disease severity. Individuals with earlier onset psoriasis are more likely to have a family history of the disease and tend to experience a more severe disease course compared with those who develop psoriasis later in life (Henseler and Christophers, 1985). Research has yet to identify external triggers for psoriasis for most instances of the disease. For individuals with a family history of psoriasis, and thus a presumed genetic susceptibility, triggering factors may include trauma to or irritation of the skin, including scratching, piercing, and sunburn; infections, particularly streptococcal upper respiratory infections in children (Besgen et al., 2010; Rasmussen, 1986); cigarette smoking (Armstrong et al., 2015; Naldi, 2016); certain medications, including interferon, lithium, and antimalarials

(Armstrong and Read, 2020; Boehncke and Schön, 2015); and metabolic and psychological stress (Armstrong et al., 2015; Rigas et al., 2019).

### Diagnostic Tools

Clinical findings and family history are the primary diagnostic indicators of psoriasis. Clinicians will conduct a full body exam, paying particular attention to the skin and nails, and rely on a scoring system, such as the Psoriasis Global Assessment scale, Psoriasis Area and Severity Index, or the Lattice System Physician's Global Assessment instrument (Langley and Ellis, 2004), to diagnose psoriasis and assess its severity, though they may also order a skin biopsy for atypical presentations of the disease (Armstrong and Read, 2020). Confounding conditions can include other inflammatory, infectious, and neoplastic conditions such as atopic dermatitis, seborrheic dermatitis, pityriasis rosea, syphilis, and cutaneous T-cell lymphoma.

### Treatments and Prospects for Cures

Treatment options for psoriasis are based on the severity of the disease and whether the individual also has psoriatic arthritis. Corticosteroids, vitamin D analogs, calcineurin inhibitors, keratolytics, and targeted phototherapy are common options for mild psoriasis affecting less than 3 to 5 percent of the body surface area (Armstrong and Read, 2020). A meta-analysis of published research found that corticosteroids combined with vitamin D<sub>3</sub> improves psoriasis of the scalp, but further research is needed to inform safety and long-term maintenance treatment (Mason et al., 2013). Recommended treatments for moderate to severe psoriasis include biologics and oral agents, including methotrexate, apremilast, acitretin, and cyclosporine, combined with phototherapy (Martin et al., 2019). While oral agents were previously the treatment of choice for plaque psoriasis, TNF inhibitors, IL-12/23 inhibitor, IL-17 inhibitors, and IL-23 inhibitors since have proven to be more effective treatments (Feldman, 2021). FDA has also approved biological agents such as these for treating psoriatic arthritis (Armstrong and Read, 2020). However, a large study of patients with psoriasis who were treated with systemic therapies found that those treated with biologics were at a significantly increased risk for serious infections, particularly skin and soft tissue infections, compared with patients not undergoing biologics therapy (Dobry et al., 2017). One recent study found that Black individuals were less likely to receive new therapies for psoriasis (Bell et al., 2020).

### Animal Models

There are few animal models for studying the etiology of psoriasis. Developing new diagnostics and treatments for psoriasis would benefit from developing highly predictive animal models (Bocheńska et al., 2017).

### Research Progress and Gaps

Over the past decade, there have been considerable advances in the understanding of the pathogenesis of psoriasis and in the treatment of its heterogeneous manifestations. In particular, biologics for the treatment of moderate to severe plaque psoriasis have been a significant therapeutic advancement. Remaining research gaps include a need for further understanding of the mechanistic links between psoriasis, other autoimmune diseases, and comorbid diseases (Boehncke and Schön, 2015). There exists a particular gap in the early identification of psoriatic arthritis. A deeper understanding of environmental triggers for psoriasis is also needed. Epidemiologic data across the life course in persons with psoriasis is limited, as is research addressing patient-centered personalized care for each individual living with the disease. Studies of the socioeconomic impact of psoriasis are also lacking (Boehncke and Schön, 2015). As noted above, developing better animal models could contribute to advances in psoriasis treatments.

## INFLAMMATORY BOWEL DISEASE

Ulcerative colitis and Crohn's disease are two forms of the chronic idiopathic inflammatory disorder of the gastrointestinal tract known as IBD. The main symptoms of ulcerative colitis, which damages the mucosal layer of the rectum and colon, are diarrhea, rectal bleeding, passage of mucus, crampy abdominal pain, and a feeling that a bowel movement is imminent even though the bowels are empty. In most cases, symptoms are present for weeks to months before an individual seeks medical attention, though acute cases can occur. The extent of the disease—how much of the colon is affected—correlates with the severity of these symptoms. Ulcerative colitis almost always involves the rectum and often extends proximally to involve additional areas of the colon (Rubin et al., 2019).

Crohn's disease involves the entire thickness of the wall of any part of the gastrointestinal tract rather than just the mucosal layer of the colon and bowel, and it usually presents as acute or chronic bowel inflammation. Localized inflammation in the gastrointestinal tract and the formation of

fistula tracts that can lead to fibrosis and narrowing of the intestines are two main characteristics of Crohn's disease. Population-based conducted in Norway and Minnesota suggest that "Crohn's disease presents with ileal, ileocolonic, or colonic disease in roughly one-third of patients each, and that only a small minority of patients (6–14 percent) will have a change in disease location over time" (Lichtenstein et al., 2018).

The inflammatory process in Crohn's disease proceeds along one of two pathways, one leading to a pattern of obstructive fibrosis, the other in a pattern of penetrating fistulas. The treatment and prognosis differs for each of these patterns. Crohn's disease, unlike ulcerative colitis, rarely affects the rectum (Lichtenstein et al., 2018), although a third of cases involve the area around the anus. Most often Crohn's disease is patchy—it skips areas in the diseased intestine, whereas ulcerative colitis affects continuous regions—and in rare cases, Crohn's disease can involve the liver and pancreas (Fousekis et al., 2018; Lichtenstein et al., 2018).

### Epidemiology and Impact

Information on disparities in the epidemiology of IBD can be found in Box 3-6.

**BOX 3-6**  
**IBD: Sex, Age, Racial, and Ethnic Disparities**

- Incidence of IBD is highest in White individuals and people of Ashkenazi Jewish descent
  - The incidence of IBD is increasing in Hispanic and Asian populations (Hou et al., 2009; Santos et al., 2018)
  - Incidence of Crohn's disease among women and men was about the same in a predominantly White population in Olmsted County, Minnesota
  - The incidence of ulcerative colitis was slightly higher for males than females (Shivashankar et al., 2017)
- The highest incidence of both ulcerative colitis and Crohn's disease occurs in the second to fourth decades, and particularly in the 20–29 age range
- Incidence of IBD is rising in developing countries and urban areas (Benchimol et al., 2017; Bernstein et al., 2019)
  - Prevalence is higher in urban areas and higher socioeconomic populations compared with rural areas and lower socioeconomic populations (Benchimol et al., 2017; Bernstein et al., 2019)
  - Dietary changes that affect the intestinal microbiota, exposure to sunlight or temperature differences, socioeconomic status, and hygiene are among the environmental variables most likely to explain geographic variability (Benchimol et al., 2017; Bernstein et al., 2019)
- Pediatric IBD accounts for approximately 25 percent of cases, and 18 percent of children with IBD will present before age 10 (Rosen et al., 2015)
  - Prevalence in children under age 17 increased from 33 per 100,000 in 2007 to 77 per 100,000 in 2016 (Ye et al., 2020)
  - Prevalence of Crohn's disease in children is 45.9 per 100,000 versus 21.6 per 100,000 for ulcerative colitis (Ye et al., 2020)
  - Genetic mutations increase susceptibility in 10 percent of infantile or very-early-onset cases (Ouahed, 2021).
- IBD is a familial disorder in up to 12 percent of those affected; the strongest risk factor is a first-degree relative with the disease.
  - There is about a 4-fold increased risk of ulcerative colitis and an almost 8-fold increased risk of Crohn's disease in the children of parents with ulcerative colitis (Agrawal et al., 2021a; Moller et al., 2015); similar patterns exist regarding which parts of the intestinal system the disease affects
  - Some children of parents with IBD develop disease during the first decade of life.
  - There is a 38 to 58 percent concordance in identical twins with Crohn's disease compared with a 4 percent concordance for fraternal twins, and a 6–18 percent concordance in identical twins with ulcerative colitis compared with a 0–2 percent concordance in fraternal twins (Bengtson et al., 2010; Halfvarson et al., 2003; Spehlmann et al., 2008)

### *Complications, Other Morbidity, and Long-Term Consequences*

IBD can co-occur with other autoimmune diseases including primary biliary cholangitis and celiac disease (Koulentaki et al., 1999; Oxford et al., 2013). Complications include an increased risk of depression and anxiety (Byrne et al., 2017), cardiovascular disease, stroke, and maternal and fetal complications (Agrawal et al., 2021b; Card et al., 2021; Chen and Wang, 2021; Choi et al., 2019; Odufalu et al., 2021). There is an increased risk of colon cancer in individuals with Crohn's disease or ulcerative colitis in whom one-third or more of the colon is involved (Friedman et al., 2001, 2008). With immunosuppressive treatment, there is an increased risk of lymphoma, melanoma, non-melanoma skin cancers, and infections (Chupin et al., 2020; Long et al., 2012; Mill and Lawrence, 2014).

Up to one-third of patients with IBD have at least one extraintestinal disease manifestation, which can include rheumatologic disorders, metabolic bone disorders, dermatologic disorders, and urologic disorders (Barberio et al., 2021; Rogler et al., 2021; Sange et al., 2021; Shah et al., 2021).

### *Economic Impact*

One study has estimated the total lifetime cost of IBD, as well as the difference between the costs associated with patients with IBD versus matched controls, using the Truven Health MarketScan insurance claims database for the period 2008 to 2015<sup>3</sup> (Lichtenstein et al., 2020). Compared with matched controls, patients with Crohn's disease diagnosed at any age incurred \$416,352 in additional costs. For those diagnosed from birth to age 11, the additional costs totaled over the lifetime averaged \$707,111, and those diagnosed at age 70 or older incurred an average of \$177,614 in additional costs over their lifetime. The average total lifetime cost for patients of all ages was \$622,056–\$273,056 for outpatient expenses, \$164,298 for inpatient services, \$163,722 in pharmacy billings, and \$20,979 for emergency department visits.

Compared with matched controls, patients with ulcerative colitis diagnosed at any age incurred \$230,102 in additional costs over their lifetimes. For those diagnosed from birth to age 11, the additional costs totaled over the lifetime averaged \$369,955, and those diagnosed at age 70 or older incurred an average of \$132,396 in additional costs over their lifetime. The average total lifetime cost for patients of all ages was \$405,496–\$163,670 for outpatient expenses, \$123,190 for inpatient services, \$105,142 in pharmacy billings, and \$13,493 for emergency department visits. Taken together, individuals with IBD will incur a total of \$875 billion in lifetime

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<sup>3</sup> Adjusted to 2016 U.S. dollars.

costs, \$498 billion for those with Crohn's disease and \$377 billion for those with ulcerative colitis.

### Risk Factors and Etiology

Epidemiologic studies have identified a variety of potential risks factors for developing IBD. For example, infectious gastroenteritis increases the risk of developing IBD by two- to three-fold (Acheson and Truelove, 1961; Barclay et al., 2009; Klement et al., 2004; Ng et al., 2015). In general, research has found associations between increased risk of developing IBD and low intake of fiber (Ananthakrishnan et al., 2013; Hou et al., 2011) and high intake of sweetened beverages (Racine et al., 2016); animal proteins, particularly red and processed meat; total fats; and polyunsaturated fatty acids, including both omega-6 and omega-3 fatty acids (Hou et al., 2011; Jantchou et al., 2010; Lewis and Abreu, 2017). The risk of being diagnosed with IBD before the ages of 10 and 20 years is 3 times and 1.6 times higher, respectively, for individuals who experience an infection during the first year of life (Bernstein et al., 2019). Sleep disruption has been shown to increase both the incidence and relapse of IBD (Ballesio et al., 2021; Beilman et al., 2020). Other risk factors include use of nonsteroidal anti-inflammatory medications, urbanization, and environmental pollution. Breastfeeding appears to be a protective factor for IBD development in children, with a longer period of breastfeeding providing greater protection (Barclay et al., 2009; Klement et al., 2004; Ng et al., 2015). While smoking is associated with a decreased risk of ulcerative colitis irrespective of race or ethnicity, it is associated with an increased risk of Crohn's disease in non-Jewish White smokers (Piovani et al., 2021).

Research suggests that IBD arises because of a dysregulated response to commensal microbes within the intestine, though it is also affected by a complex interplay of host genetic risk, aberrant immune responses, and environmental factors. The mucosal immune system is altered in IBD and is characterized by an abundance of proinflammatory mediators from cells associated with adaptive immunity, such as T helper cells, and innate immunity, including macrophages and dendritic cells, which occur in increased numbers in mucosa affected by IBD. There is evidence that non-immune cells, such as epithelial and stromal cells, are also reprogrammed in IBD and play a significant role in the propagation of dysregulated immune responses. Historic paradigms regarding differential T helper cell responses in Crohn's disease versus ulcerative colitis have evolved with the use of large-scale and multidimensional immunophenotyping of human tissue. The diseases seem to share many common immunological features (Chang, 2020; Mitsialis et al., 2020; Peterson and Artis, 2014).

As mentioned above, a number of rare single genetic mutations have been identified as the basis of susceptibility in up to 10 percent of cases of infantile IBD or very-early-onset IBD, suggesting a simple monogenic origin of the disease in these cases (Ouahed, 2021). More than 60 different gene defects have been identified in patients with very-early-onset IBD by whole exome sequencing. However, IBD in the majority of pediatric and adult patients involve the interplay of multiple genes with other factors (Nambu et al., 2021).

### Diagnostic Tools

Clinicians use several diagnostic tools to assess disease activity and extent in IBD, including sigmoidoscopy before deciding the course of treatment for ulcerative colitis, and colonoscopy to determine the extent of disease in patients who are not having an acute flare (Pabla and Schwartz, 2020). Histology can provide information to grade activity in ulcerative colitis, though histologic features change more slowly than clinical features. There are also a number of abnormalities in Crohn's disease that show up in laboratory tests, including levels of erythrocyte sedimentation rate and C-reactive protein, as well as hypoalbuminemia, anemia, and leukocytosis in more severe cases (Cappello and Morreale, 2016). Levels of the fecal proteins calprotectin and lactoferrin can distinguish IBD from irritable bowel syndrome,<sup>4</sup> determine whether ulcerative colitis and Crohn's disease are active, and detect whether Crohn's disease has returned after surgery to remove the diseased portion of the intestines (Zhou et al., 2014). Studies have not found antibodies to be that useful in diagnosing IBD, though there is some evidence that increased levels of anti-*Saccharomyces cerevisiae* antibody may be indicative of Crohn's disease and that elevated levels of perinuclear antineutrophil cytoplasmic antibody may occur more frequently in people with ulcerative colitis (Mitsuyama et al., 2016). However, antibody levels tend to be relatively insensitive to and nonspecific for IBD given that they are often elevated in other autoimmune diseases, infections, and inflammatory conditions, including those outside of the gastrointestinal tract (Kyriakidi et al., 2016; MedlinePlus, 2021; Roozendaal and Kallenberg, 1999).

### Treatments and Prospects for Cures

Initial therapy for people with moderate to severe Crohn's disease and ulcerative colitis usually includes biologic and small molecule

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<sup>4</sup> Irritable bowel syndrome is the term for symptoms that occur when the contents of the large intestine move too quickly or too slowly.

therapy, with the goal of maintaining remission and preventing future complications. High-risk people with ulcerative colitis who are more likely to require biologics-based treatment include those with moderate to severe disease, steroid-dependent or steroid-refractory disease, and refractory inflammation of the ileoanal J pouch. High-risk people with Crohn's disease who are more likely to require biologics include those who are younger than 30 and have extensive disease, with perianal or severe rectal disease and/or deep ulcerations in the colon and stricturing or penetrating disease behavior. The current goal of IBD treatment is to treat early in the disease course, treat aggressively with top-down biologics therapy, check drug and drug metabolite levels, administer dual therapy with immunomodulators and biologics in appropriate patients, and aim for deep remission as assessed by endoscopy and histology. Studies have shown that biologic therapies produce marked improvements in clinical symptoms and allow patients with IBD to enjoy a better quality of life with less disability, as well as fewer hospitalizations and surgeries (Al-Bawardy et al., 2021; Armuzzi and Liguori, 2021; Singh et al., 2020).

Diet plays a significant role in shaping the gut microbiome, and one theory holds that dietary components interact with the microbiome and stimulate a mucosal immune response. In fact, active Crohn's disease responds to exclusive enteral nutrition or bowel rest with total parenteral nutrition (TPN), which have been shown to be as effective as glucocorticoids in inducing remission but are not as effective for maintenance therapy. This lends further support to the theory that dietary antigens stimulate an immune response. In contrast with Crohn's disease, elemental diets or TPN are not effective treatments for ulcerative colitis.

Dietary approaches as maintenance therapy in Crohn's disease have been adapted largely from findings of epidemiologic studies; however, there is significant heterogeneity among research studies. The overall dietary approach is to maximize fiber intake, particularly from fruits and vegetables, and to limit consumption of higher-risk foods. There are several defined diets that generally adhere to these principles with some variation. These diets include the Mediterranean diet pattern, Specific Carbohydrate Diet, Semi-Vegetarian Diet, and IBD Anti-Inflammatory Diet. However, much work remains to understand how diet might affect disease risk and activity, research that may eventually lead to evidence-based nutrition guidelines.

Therapies targeting specific cytokines, such as TNF, IL-12, and IL-23, have revolutionized IBD treatment. Therapy targeting immune cell trafficking to intestinal tissue has proven successful in IBD and shows continued promise. However, the cumulative repertoire of therapies for IBD is limited and many people with the condition suffer with refractory disease.

## Animal Models

There are four categories of animal models of intestinal inflammation—chemical, genetically engineered, cell transfer, and congenic—that researchers use to study how IBD develops and explore new therapeutic approaches (Bamias et al., 2017). Chemical models, which researchers create by using harsh chemical to damage the colon, provide insight into early repair mechanisms, but not for studying the inflammatory processes active in IBD. Creating genetic engineering models involves either deleting genes that control the production of one or more proteins they suspect play a role in disease development or introducing mutations that lead to overproduction of those proteins. Such models are useful for studying specific pathways in the inflammatory response, but not for studying the complex interaction of different pathways that characterize both a normal and abnormal immune response.

Cell transfer models involve injecting different subsets of T cells from a donor into specially bred mice that lack adaptive immunity and that have been kept in germ-free environments. Researchers use cell transfer molecules to study the protective or pathogenic roles that specific types of T cells play in mucosal immunity, but because the animals are immunodeficient, unlike humans with IBD, the insights gained from these studies may not apply fully to IBD. Congenic models develop disease spontaneously as a result of specific breeding, genetic, or housing backgrounds. These models most closely recapitulate human disease, but they are hard to develop and the most complex to study. Efforts to develop safe and effective treatments for IBD could benefit from the development of additional animal models.

## Research Progress and Gaps

Researchers have made progress in many areas of IBD, particularly in terms of developing effective biologic therapies and other therapeutic approaches for IBD. There has been progress in diagnosis such as using specialized MRI, computed tomography, video capsule technology, and colonoscopic evaluation. There have also been advances in identifying immunologic and environmental factors that may predispose an individual to developing IBD, as well as genetic factors involved in very-early-onset IBD.

Research gaps for IBD include the need to establish a more complete knowledge of disease etiology and pathogenesis and the influence of genetic predisposition and environmental factors on disease development and phenotype. Research is also needed to identify how to prevent onset of disease in a person with a strong familial risk. There is a large gap in

epidemiological data on IBD, including incidence and prevalence in the United States and well-designed studies that would provide a better picture of disease risk in the U.S. population.

Among the key needs are developing better biomarkers to monitor disease activity and determining the causes of disease flares and how to prevent them. Identifying the specific biological pathways that result in the observable characteristics and symptoms of IBD would enable matching effective medications to specific IBD manifestations. In addition, evaluating the efficacy of alternative and complementary therapies such as diet, stress-reduction, and nutritional supplements would represent an advance. Other useful research areas assess the safety of administering biologics and the thiopurine family of immunosuppressive drugs to individuals with IBD—during pregnancy in mothers and prior to conception in fathers—as well as determining the long-term health effects to the offspring (Kanis et al., 2017). Creating new animal models that define the safety and efficacy of novel therapeutic strategies for IBD could support advances in understanding of the disease.

## CELIAC DISEASE

Chronic inflammation of the intestines, caused by the immune system's reaction to dietary gluten, is the characteristic feature of celiac disease, sometimes called celiac sprue or gluten-sensitive enteropathy. Over time, this immune response destroys the intestinal mucosa, which hampers absorption of nutrients from the intestines and can cause diarrhea, fatigue, weight loss, bloating, constipation, and anemia. In children, malabsorption can affect growth and development (Lebwohl et al., 2018). In addition, the intestinal damage that arises in celiac disease can result in serious complications, described further below (Mayo Clinic, 2021a).

### Epidemiology and Impact

Information on disparities in the epidemiology of celiac disease can be found in Box 3-7.

**BOX 3-7****Celiac Disease: Sex, Age, Racial, and Ethnic Disparities**

- 1.5 times more common in females than in males, and approximately 2 times more common in children than in adults (Singh et al., 2018)
- Prevalence and incidence has been increasing over time; changing environmental factors may be influencing disease development (Lohi et al., 2007; Ludvigsson et al., 2013)
- Prevalence in Europe and Oceania, 0.8 percent; Asia, 0.6 percent; Africa, 0.5 percent; North America, 0.5 percent; South America, 0.4 percent (Singh et al., 2018)
- U.S. prevalence is 4–8 times higher among non-Hispanic Whites compared with other racial and ethnic groups (Mardini et al., 2015).

*Complications, Other Morbidity, and Long-Term Consequences*

Individuals with celiac disease typically have co-occurring autoimmune conditions such as type 1 diabetes, IBD, Hashimoto's thyroiditis, Graves' disease, primary biliary cholangitis, scleroderma, SLE, and dermatitis herpetiformis, an autoimmune blistering skin (Cohn et al., 2014; Fröhlich-Reiterer et al., 2008; Kahaly et al., 2018; Kurien et al., 2016; Lebwohl et al., 2021; Márquez and Martin, 2021; Pascual et al., 2014; Regev et al., 2021; Yang et al., 2005). When left untreated, celiac disease has significant associated morbidity, including anemia, folate and B12 deficiency, osteopenia and osteoporosis, gastrointestinal lymphoma, dental enamel defects, neurologic complications such as peripheral neuropathy and cerebellar ataxia, infertility, and growth retardation in children (Caio et al., 2019; Catassi et al., 2005; Green et al., 2003; Jericho et al., 2017; Kupfer and Jabri, 2012; Lebwohl et al., 2018; Leonard et al., 2017; Lundin and Wijmenga, 2015; Rubio-Tapia et al., 2013; Salem and Estephan, 2005; Therrien et al., 2020). In addition, persons with the disease are at an increased risk for pneumococcal infection, particularly if unvaccinated, as well as sepsis (Simons et al., 2018).

Depression and related mood disorders have been reported to be more common in patients with celiac disease compared to those without the disease (Jackson et al., 2012; Smith and Gerdes, 2012). Anxiety disorders are associated with gluten intolerance, and there are conflicting findings regarding whether a gluten-free diet decreases anxiety in patients with celiac disease (Jackson et al., 2012; Rostami-Nejad et al., 2020).

An uncommon complication is refractory celiac disease (Hujoel and Murray, 2020; Penny et al., 2020). Symptoms mimic those of severe untreated celiac disease; however, unlike celiac disease, there is no or,

at best, an incomplete response to dietary gluten withdrawal. The prognosis is uncertain for patients with refractory celiac disease, and many develop intractable nutritional deficiencies requiring long-term parenteral alimentation that may lead to complicating infections. The importance of diagnosing celiac disease-associated with these concomitant diseases is essential since a gluten-free diet is able to resolve symptoms and prevent the potentially severe long-term complications (Caio et al., 2019).

### *Economic Impact*

One study of patients with celiac disease confirmed by endoscopic biopsy estimated all-cause health costs associated with this disease over the course of 2 years (Cappell et al., 2020). Compared with health care costs for individuals without celiac disease, the average all-cause health care costs for individuals with celiac disease were \$15,687 versus \$12,220 at time zero, \$19,181 versus \$11,260 after 1 year, and \$15,355 versus \$11,579 in year two. At the start of the study, all-cause inpatient admissions costs and outpatient services costs were higher for individuals with celiac disease than for controls, but outpatient pharmacy costs were similar between the two groups. Patients with celiac disease, compared with control subjects, spent a greater percentage of their total health care costs on outpatient services (64.5 percent versus 59.4 percent) but a smaller percentage on outpatient pharmacy expenses (16.6 percent versus 22.3 percent).

### **Risk Factors and Etiology**

Celiac disease correlates strongly with specific variations in HLA genes, but that association does not fully account for the risk of developing the disease (Kuja-Halkola et al., 2016; Sciurti et al., 2018). Since almost everyone consumes dietary gluten during his or her lifetime, other environmental or other risk factors may trigger the body's lost tolerance to dietary gluten and increase the risk of developing celiac disease. Exposures occurring in utero or very early in life may be important predisposing factors, as suggested by the observation that children born during the spring and summer are at the highest risk of developing celiac disease (Namatovu et al., 2016). Research has identified several promising risk factors, including gastrointestinal infections (Kempainen et al., 2017; Lindfors et al., 2019; Stene et al., 2006) and high gluten intake in early childhood (Andrén Aronsson et al., 2019; Lindfors et al., 2019).

The development of celiac disease is complex, and multiple research studies are in progress to better understand the pathogenic process. One avenue of research is exploring the role that gliadins, key components of gluten, play in disease development. Gliadins are complex proteins that

are unusually rich in the amino acids proline and glutamine and that intestinal enzymes cannot break down completely. The final product of this partial digestion is a mix of peptides that can trigger host responses including increased gut permeability and innate and adaptive immune responses that closely resemble those instigated by the exposure to potentially harmful microorganisms (Caio et al., 2019).

### Diagnostic Tools

Many cases of celiac disease occur with neither a family history nor its classical symptoms such as chronic diarrhea and weight loss (Agardh et al., 2015; Stahl et al., 2021). Noninvasive and more sensitive screening tools have revealed celiac disease to be a heterogeneous disease (Lad and Jacobson, 2001); in fact, nonspecific symptoms often go unrecognized by clinicians and the individuals with the condition, leading to diagnostic delay (Paez et al., 2017). One study from the Netherlands, for example, used antibody testing to screen a cohort of 6-year-old children for celiac disease. This study found that screening-identified subclinical and asymptomatic individuals had a lower body mass index and lower bone mineral density than their healthy peers (Jansen et al., 2015, 2018), suggesting that the disease process is occurring before symptoms are recognized and that it would be beneficial to screen more regularly for celiac disease using both the Enzyme-linked immunoassay (ELISA)-based anti-tissue transglutaminase (tTG) immunoglobulin A (IgA) and the immunofluorescent anti-endomysium (EmA) IgA tests (Baudon et al., 2004).

In the same way that the clinical manifestations of celiac disease can vary enormously, so too can laboratory findings. Patients with atypical celiac disease often have no abnormalities in their complete blood count and comprehensive panel or merely show evidence of iron or folate deficiencies, while those with more classical presentations of the disease can have multiple lab test abnormalities such as abnormal quantities of fat in stool samples and abnormally low blood levels of albumin, the blood-clotting protein thrombin, or calcium (Lebwohl et al., 2018; Loginov et al., 1984; Meena et al., 2020; Rickels and Mandel, 2004).

Serologic tests are useful screening tests for celiac disease. Both the anti-tTG IgA and anti-EmA IgA tests have reported sensitivities of 94 to 98 percent and specificities of 91 to 100 percent (Caio et al., 2019; Leffler and Schuppan, 2010), though the sensitivities of those assays are somewhat lower in infants, toddlers, and people with mild disease. Clinicians use the anti-tTG IgA test as the initial screening test owing to its higher sensitivity (98 percent versus 95 percent), while they use the operator-dependent and more costly anti-EmA IgA test when the anti-tTG IgA test is unexpectedly negative or to confirm a positive anti-tTG IgA test (Leffler

and Schuppan, 2010; Medical Advisory, 2010; NIDDK, 2021a). Unexpected false-negative results can occur among the 2 to 3 percent of people with celiac disease who also have an IgA deficiency, in which case there are less sensitive IgG-based assays that clinicians can use (Caio et al., 2019; Rubio-Tapia et al., 2013).

Recently, both anti-deamidated gliadin peptide (DGP) IgA and IgG antibody tests have become available, though there is no evidence that anti-DGP IgA testing provides a significant advantage over anti-tTG IgA testing. On the other hand, the anti-DGP IgG test has higher sensitivity (80.0 percent) and specificity (98.0 percent) than the anti-tTG IgG test and is the serological test of choice in IgA-deficient individuals (Leffler and Schuppan, 2010; Zucchini et al., 2016).

The gold standard for celiac diagnosis remains mucosal intestinal biopsy of the bulb, the distal duodenum, or proximal jejunum combined with a clinical response to eliminating gluten from the diet of an individual suspected to have celiac disease (Freeman, 2018). The one exception to this rule pertains to children and adolescents whose anti-tTG IgA levels exceed 10 times the upper limit of normal, who are also anti-EmA positive using a separate blood sample, and who test positive for two specific celiac-associated genes, HLA-DQ2 and/or HLA-DQ8 (Kelly et al., 2015). If these criteria are met in the pediatric population, new guidelines say that clinicians can skip the biopsy prior to starting the individual on a gluten-free diet.

### Treatment and Prospects for Cures

Adhering to a gluten-free diet is standard treatment for this disease. Instead of eating products containing wheat, barley, rye, and triticale, individuals can turn to products made from rice, corn, potatoes, millet, and soybeans. Individuals with celiac disease can tolerate moderate quantities of oats, but only brands that are certified as not contaminated with wheat and other cereal grains during processing and shipping (Green and Cellier, 2007; Husby et al., 2019; Ludvigsson et al., 2014; Rubio-Tapia et al., 2013). Individuals with celiac disease may also require iron and folate supplements if laboratory tests show deficiencies in these micronutrients, and they may require calcium and vitamin D supplements if bone density measurements reveal they have osteopenia (NIH Osteoporosis and Related Bone Diseases National Resource Center, 2018; Rondanelli et al., 2019). Other aspects of care for individuals with celiac disease should include pneumococcal vaccination, especially if there is evidence of decreased spleen function (Passanisi et al., 2020), and identification of other food intolerances (Rubio-Tapia et al., 2013). Clinicians should refer

individuals with celiac disease to a dietitian familiar with this disease and to lay support groups to help them maintain gluten-free diets.

Clinicians should monitor dietary compliance every 6 to 12 months by ordering a repeat anti-tTG IgA or anti-EmA IgA test; these antibodies disappear when individuals comply fully with a gluten-free diet (Moreno et al., 2017). If symptoms do not recur, specific follow-up medical care is not necessary, aside perhaps from laboratory tests such as an annual hemoglobin or hematocrit test and bone density monitoring (Beyond Celiac, n.d.).

Research on preventing celiac disease has focused on manipulating the infant diet, based on observational studies suggesting that the timing of gluten introduction to the infant diet may affect the risk of developing the disease (Pinto-Sánchez et al., 2016). While one randomized controlled trial (RCT) in the general population found that infants who had gluten added to their diets at 4 months of age had a reduced prevalence of celiac disease compared with infants who were exclusively breastfed until 6 months of age (Logan et al., 2020), two larger RCTs in infants at risk for celiac disease found no significant effect of the timing of gluten introduction on incidence of celiac disease (Lionetti et al., 2014; Vriezinga et al., 2014).

Recently, investigators published the results of the first randomized trial of a transglutaminase 2 inhibitor (Schuppan et al., 2021). In this preliminary trial, treatment with this agent attenuated gluten-induced duodenal mucosal damage in patients with celiac disease.

### Animal Models

Researchers have developed several useful animal models of celiac disease, although none fully captures all features of disease pathology. One group developed models of spontaneous gliadin-dependent intestinal inflammation in rhesus macaques and Irish setters that produce some of the hallmarks of celiac disease (Costes et al., 2015). Researchers have also seen spontaneous inflammatory small bowel disease in horses that resolves after 6 months of a gluten-free diet (van der Kolk et al., 2012). Investigators have used gluten sensitization to study gluten-dependent intestinal inflammation conditions in mice and rats. Some of the rodent models have been used to test the immunogenicity of detoxified gluten products, while others have proven valuable for studying adaptive immune responses to gluten. Recently, researchers have developed a mouse model that overexpresses interleukin-15 (IL-15) in the gut epithelium and thin layer of connective tissue that lies beneath the epithelial layer. This model mimics the immune system features and gluten-dependent intestinal damage seen in celiac disease and suggests that location-specific expression of IL-15 plays a central role in the development of

celiac disease. This new model may prove useful for generating new knowledge about the development of celiac disease and for testing new therapeutic strategies (Abadie et al., 2020).

### Research Progress and Gaps

Celiac disease is unusual among autoimmune diseases in that research has identified the external trigger—dietary gluten—and the genetic background necessary for disease development. Even with this knowledge, though, there is currently no way to prevent the disease. Two prospective cohort studies have leveraged NIH funding and studied the genetic and environmental determinants of both type 1 diabetes and celiac disease: the Colorado-based Diabetes Autoimmunity Study in the Young, also known as DAISY,<sup>5</sup> and the multicenter international study The Environmental Determinants of Diabetes in the Young, also known as TEDDY.<sup>6</sup> In these cohorts, the investigators are monitoring autoantibodies associated with both type 1 diabetes and celiac disease frequently from birth, with a prompt referral for further medical evaluation of those testing positive. Follow-up of these cohorts is critical to understanding the life course of celiac disease and to offer clues as to how to prevent these diseases.

An additional research gap is that celiac disease remains under-diagnosed in the general population (Singh et al., 2018). Since some people have minimal symptoms, those diagnosed with celiac disease may represent the tip of iceberg. Thus, more research is needed to estimate the true incidence and prevalence in the population. Another major research gap is that there is currently no treatment for the gastrointestinal symptoms of a person with celiac disease who has inadvertently ingested gluten. The gluten-free diet is very restrictive and not all “gluten-free” labels are accurate. Inadvertent gluten ingestion can cause severe symptoms.

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<sup>5</sup> The Diabetes Autoimmunity Study in the Young (DAISY) is a prospective cohort study that enrolled 2,547 children with a high-risk HLA genotype (enrolled at birth) or a first-degree relative with type 1 diabetes (enrolled between birth and age 7 years) (Frohnert et al., 2017; NLM, 2021). The children have been monitored for over 20 years for development of type 1 diabetes-related autoimmunity.

<sup>6</sup> The Environmental Determinants of Diabetes in the Young (TEDDY) study is a prospective observational multicenter cohort study to identify infectious agents, dietary factors, or other environmental exposures that are associated with increased risk of autoimmunity and type 1 diabetes (NIDDK, 2021b). The study has enrolled 8,676 newborns who are less than 4 months old with high-risk human leukocyte antigen alleles or who are first-degree relatives of patients affected with type 1 diabetes. The children are followed up for 15 years.

## PRIMARY BILIARY CHOLANGITIS

PBC (previously called primary biliary cirrhosis) is an immune-mediated chronic disease that slowly destroys the bile ducts in the liver. Persons affected are commonly asymptomatic at presentation; however, they may experience fatigue or symptoms of cholestasis such as itching skin or fatty stool, or symptoms of cirrhosis such as hypertension of the portal vein leading to the liver, or ascites, fluid collecting in the abdomen that can be painful when severe (Civan, 2019; Mayo Clinic, 2021d). Individuals with PBC can develop cirrhosis and liver failure and may require liver transplantation.

### Epidemiology and Impact

Information on disparities in the epidemiology of PBC can be found in Box 3-8.

#### BOX 3-8 PBC: Sex, Age, Racial, and Ethnic Disparities

- Women account for approximately 90 percent of all cases (Carey et al., 2015)
- Typical age of onset is in fifth or sixth decades of life (Carey et al., 2015)
- Incidence and prevalence are highest in northern Europe and northern United States (Lv et al., 2021)
- Increased prevalence among some U.S. and Canadian Indigenous populations (Yoshida et al., 2006)
  - Severity of disease may be greater in Canadian Indigenous populations with worse long-term outcomes (Roberts et al., 2022)
- Prevalence is highest among White, Asian, and Pacific Islander populations compared to Black populations (Lu et al., 2018)
  - Severity of disease at diagnosis may be greater in Black and Hispanic compared with White populations (Peters et al., 2007).

### *Complications, Other Morbidity, and Long-Term Consequences*

Individuals with PBC may experience severe, long-term consequences resulting from complications related to chronic reduction in bile flow, including osteoporosis, itchy skin, hyperlipidemia, fatigue, and sicca syndrome, one form of which is Sjögren's disease. A deficiency of fat-soluble vitamins may occur in persons with PBC, particularly in those with advanced-stage disease. Vitamin A deficiency can also occur in up to one-third of those with the disease, and cases of night blindness have been reported (Phillips et al., 2001; Waqr et al., 2010). Complications related to cirrhosis include hepatocellular carcinoma and portal hypertension as well as susceptibility to a variety of infections (Bajaj et al., 2021). Clinicians normally refer patients with end-stage PBC for liver transplantation (Carey et al., 2015; Lindor et al., 2019).

Fatigue is a major complaint in individuals with PBC, affecting approximately 50 percent of those with the disease, and 20 percent are affected in significant or life-changing ways (Jopson and Jones, 2015). Self-reported anxiety and depression or depressive symptoms are also common (Sivakumar and Kowdley, 2021; Zenouzi et al., 2018), and a large population study found that depression and fatigue have a significant effect on perceived quality of life in persons with PBC (Mells et al., 2013).

### *Economic Impact*

One study estimated the average all-cause cost of inpatient medical care for individuals with PBC to be \$3,905 per patient per month (Primary biliary cholangitis: Patient characteristics and the health care economic burden in the United States, 2021), of which 66 percent, or an average of \$2,577 per patient per month, was attributed to PBC. This study also estimated the average total cost for all health care for individuals with PBC to be \$6,568 per patient per month.

Researchers have also examined the cost effectiveness of obeticholic acid (OCA) therapy (Samur et al., 2017) using a mathematical model to simulate the lifetime course for patients with PBC treated with OCA plus ursodeoxycholic acid (UDCA) versus UDCA alone. This analysis estimated that OCA plus UDCA could reduce severe disease over the course of 15 years. Cumulative incidence of decompensated cirrhosis would decrease from 12.2 percent of individuals treated with UDCA alone to 4.5 percent, hepatocellular carcinoma would decrease from 9.1 percent to 4.0 percent, and liver-related deaths would decrease from 16.2 percent to 5.7 percent. The need for liver transplants would decrease by nearly 75 percent, from 4.5 percent of individuals with PBC to 1.2 percent, and transplant-free survival would increase from 61.1 percent to 72.9 percent. While the lifetime cost of adding OCA to the treatment regimen would

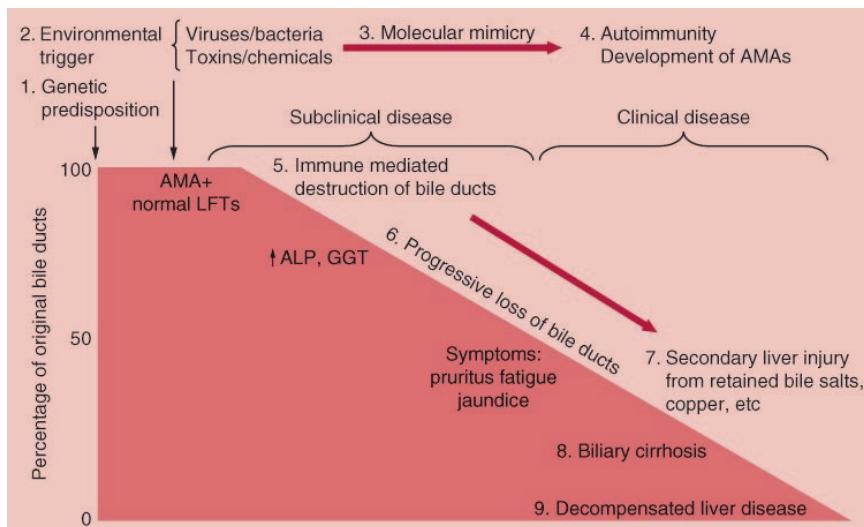
increase from \$63,000 to \$902,000, the analysis estimated that the incremental cost-effectiveness ratio for the combination therapy would be \$473,400 per quality-adjusted life year gained.

### Risk Factors and Etiology

PBC develops through the combined effects of genetics, environment, and autoimmunity. A family history of PBC or of other autoimmune diseases and a history of smoking are among the risk factors for PBC (Smyk et al., 2012; Tanaka et al., 2018). The first-degree relatives of people with PBC have a 10-fold higher prevalence of disease than the general population, and PBC has the highest reported concordance rate (63 percent) in identical twins of any autoimmune disease (Webb et al., 2015). The prevalence of anti-mitochondrial autoantibodies, a biomarker for PBC, in the first-degree relatives of persons with PBC is 13.1 percent compared with 1 percent in controls (Lindor et al., 2019).

Research has identified several possible environmental triggers for PBC, including infectious agents and industrial pollutants that have significant homology with human mitochondrial proteins (Gershwin et al., 2005; Juran and Lazaridis, 2014). Other potential triggers include cosmetic products such as nail polish and lipsticks (Tanaka et al., 2018). Several studies have found an association between PBC and urinary tract infections caused by *Escherichia coli* (Koutsoumpas et al., 2014; Wang et al., 2014), while the evidence suggesting that environmental toxins may trigger PBC comes from geographical clustering of PBC cases around areas of toxic waste disposal and in low-income areas (Juran and Lazaridis, 2014). Exposure to these triggers may thus lead to the immune system losing self-tolerance against the homologous human proteins, which results in persistent T cell-mediated destruction of the intrahepatic bile ducts and injury from accumulating bile salts. Over time, this damage can lead to biliary cirrhosis and decompensated liver disease (Figure 3-1).

Older age and measures of poorer liver function at diagnosis are associated with a higher mortality risk from PBC (Lu et al., 2018), while histologic stage of the disease predicts survival. One study measuring the rate of histologic progression found that the average time for individuals with PBC to develop extensive fibrosis was 2 years, with only a 29 percent probability of stabilizing in early-stage PBC after 4 years. This study also found that 50 percent of the individuals who only had what is known as interface hepatitis without fibrosis developed cirrhosis within 4 years, and only 20 percent of the pre-cirrhotic individuals were histologically stable. The average rate of histologic stage progression was one stage every 1.5 years (Lindor et al., 2019).



**FIGURE 3-1** Pathogenesis and natural history of PBC.

NOTE: ALP, alkaline phosphatase; AMA, anti-mitochondrial antibody; GGT,  $\gamma$ -glutamyl transferase; LFTs, liver function tests.

SOURCE: Pratt, 2016.

### Diagnostic Tools

PBC presents in a heterogeneous fashion; about 50 percent of people are asymptomatic at diagnosis (Khanna et al., 2018). In one population based study, approximately half of patients who were initially asymptomatic developed symptoms within 5 years of PBC diagnosis, and only 5 percent remained symptom free after 20 years (Prince et al., 2004). An incidental finding of elevated alkaline phosphate, abnormally low bile flow, or a positive test for anti-mitochondrial antibody after screening for autoimmune extrahepatic disease are the common ways in which clinicians initially identify individuals with PBC (Hirschfield, 2017; Lindor et al., 2019). Clinicians will confirm a PBC diagnosis when two of the following three criteria are met: assays suggesting that bile flow is reduced or absent, the presence of anti-mitochondrial antibodies, and histology results indicating inflammation of the interlobular bile ducts that does not involve pus formation. Elevated bilirubin levels suggest more advanced disease is present, and while aminotransferases can be elevated, the pattern of liver injury is predominantly related to reduced or absent bile flow (Hirschfield, 2017; Lindor et al., 2019).

Anti-mitochondrial antibodies are present in 90 to 95 percent of those diagnosed with PBC (Colapietro et al., 2021). The presence of this autoantibody, which is involved in T cell-mediated destruction of the bile ducts, precedes biochemically apparent liver injury by several years. Individuals with PBC may also test positive for antinuclear and other autoantibodies, though their diagnostic utility is limited because of poor sensitivity (de Liso et al., 2018).

Once there is biochemical evidence of reduced or absent bile flow—via an elevated level of alkaline phosphatase and often a concurrently elevated level of 5'-nucleotidase and gamma-glutamyl transpeptidase—clinicians order noninvasive imaging of the liver and biliary tree to rule out a biliary obstruction. Direct bilirubin is elevated in later stages of the disease. In the event of an unclear diagnosis, clinicians may pursue X-ray or MRI examination of the bile ducts; in some instances, it may be necessary to conduct an endoscopic evaluation of the bile ducts.

Noninvasive transient elastography, which measures liver stiffness, has proven to be highly accurate at diagnosing advanced fibrosis in individuals with PBC. Progressive liver stiffness in PBC is predictive of a poor outcome (Lindor et al., 2019). Liver stiffness increases markedly over a 5-year period in treated individuals with cirrhosis and PBC; in treated individuals without cirrhosis, however, stiffness usually remains stable (Lindor et al., 2019). One study found that individuals with a liver stiffness of greater than 9.6 kilopascals—the normal range is 2 to 6 kilopascals—were five times more likely to result in clinical decompensation, death, or liver transplantation (Corpechot et al., 2012).

### Treatments and Prospects for Cures

UDCA is the first-line therapy for PBC (Poupon et al., 1997), and clinical trials have shown that UDCA therapy improves liver biochemistries, improves survival, and reduces the need for liver transplantation (Figure 3-2) (Carey et al., 2015; Lindor et al., 2019). Individuals with early-stage PBC typically respond better to UDCA than those with advanced disease; however, even in individuals with advanced disease, treatment with a UDCA dosage of 13–15 milligrams per kilogram of body weight per day may improve survival and eliminate the need for liver transplantation (Corpechot et al., 2000; Lindor et al., 1994; Poupon et al., 1994). UDCA therapy may also reduce serum low-density lipoprotein cholesterol levels and slow histologic progression (Corpechot et al., 2000; Poupon et al., 1993), but it does not improve fatigue, itchy skin, associated bone disease, or autoimmune features that can accompany PBC (Lindor et al., 2019).

Clinical guidelines state that clinicians should assess the biochemical response after 1 year of UDCA therapy, with liver biopsy being

**EFA-approved treatments, standard of care**

- Ursodeoxycholic acid (UDCA) at 13–15 mg/kg per day, patients with improved prognosis.<sup>42,67</sup>
- Obeticholic acid (OCA) as second-line combination treatment for suboptimal UDCA responders in compensated liver disease and/or as monotherapy for patients who cannot tolerate UDCA in Child-Pugh A. Caution and dose-reduction is advised in decompensated liver disease (Child-Pugh B/C). OCA is a farnesoid X-receptor (FXR) agonist.<sup>27,74,75,79,89</sup>

**Unproven treatments**

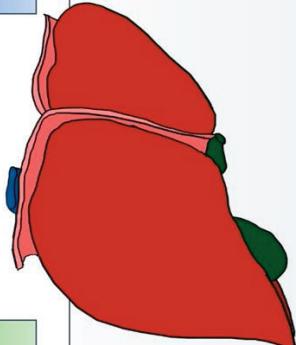
- Methotrexate has an unclear role in management of PBC, some trials have used it in conjunction with UDCA in patients with incomplete response to UDCA, but found no overall survival free of liver transplantation compared to placebo. Has been shown to be effective in PBC-AIH overlap syndrome.<sup>105</sup>
- TNF-alpha inhibitors have an unclear role in managing PBC. Many studies are single-center or case-report series, but can be indicated if patient has inflammatory bowel disease or other rheumatologic conditions.<sup>105,108</sup>

**Toxic/ineffective therapies**

Azathioprine, cyclosporine, penicillamine, prednisolone, ustekinumab.

**Investigational, novel classes**

- Peroxisome proliferator activated receptor alpha (PPAR- $\alpha$ ) agonists, also known as fibrates such as fenofibrate and bezafibrate. These have choleretic and anti-inflammatory effects with decrease in immunoglobulin-M. Positive findings in the BEZURSO study but lacking large RCTs. Regulates bile acid synthesis and modulates phospholipid secretion which protects bile duct epithelium. Elafibranor has recently demonstrated anticholestatic effects in its Phase 2 trial in Europe.<sup>82,103,104</sup>
- Peroxisome proliferator activated receptor gamma (PPAR- $\gamma$ ) agonists, such as seladipar (MBX-8025) controls genes involved in bile acid homeostasis that is expressed in hepatocytes, cholangocytes, hepatic stellate cells, and Kupffer cells. Phase 2 trial shows decrease in ALP (vs. placebo), but an increase in ALT and further studies are now held because of worsening histology observed in NASH patients.<sup>94,95</sup>
- Apical sodium-dependent bile acid transporter (ASBT) inhibitors works by blocking the enterohepatic circulation of bile acids.<sup>97,98,109</sup>
- Fibroblast growth factor -19 (FGF19) analogues Endocrine hormone that regulates bile acids and regulating hepatic cell proliferation which is also implicated in tumor formation. A synthetic FGF19 analog (NGM282, phase 2 trial) can target bile acid homeostasis, but not the proliferative function.<sup>51</sup>
- Immunomodulators small studies have shown that rituximab may abrogate cholangitis by depleting B cells, though no differences were seen in aminotransferases.<sup>99,100</sup>



**FIGURE 3-2** Medications for PBC.  
SOURCE: Galoosian et al., 2020.

uninformative (Lindor et al., 2019). Bilirubin level is strongest indicator of survival after treatment with UDCA, with alkaline phosphatase levels also being a predictor of survival (Hirschfield, 2017). Positive response to UDCA therapy is typically evident with a few weeks, with 90 percent of the improvement occurring in 6 to 9 months and 20 percent of those treated with UDCA having normalized liver biochemistries after 2 years of treatment (Lindor et al., 2019). Life expectancy for individuals whose bilirubin and alkaline phosphatase levels return to normal after treatment (Hirschfield, 2017; Hohenester et al., 2009).

In 2016, FDA approved OCA for individuals who cannot tolerate UDCA, and in combination with UDCA for the treatment of individuals who do not have an adequate response to UDCA alone after 1 year of treatment (Krupa et al., 2022). In September 2017, FDA issued a warning regarding the use of OCA in patients with moderate to severe liver impairment following reports that OCA was associated with worsening PBC and death (FDA, 2017b). In May 2021, FDA restricted the use of OCA in patients that have PBC with advanced cirrhosis of the liver due to the potential for serious harm, such as advanced liver decompensation or liver failure, that can be attributed to starting OCA (FDA, 2021b).

OCA modulates bile acid synthesis, absorption, transport, secretion, and metabolism with the net effect of increasing the flow of bile from the liver (FDA, 2018b; Hirschfield et al., 2015). There is some evidence from animal models that OCA might have antifibrotic and anti-inflammatory activity. While clinical trials assessing whether OCA has an effect on survival of individuals with PBC are in progress, simulation models suggest that combined UDCA and OCA therapy could decrease the 15-year cumulative incidences of decompensated cirrhosis, hepatocellular carcinoma, liver transplants, and liver-associated mortality (Samur et al., 2017).

Studies have shown that fibrates, medication prescribed to lower high triglyceride levels, can reduce bile acid synthesis and increase production of bile acid transporter molecules. As a result, studies have evaluated fibrates for treating PBC and found them to be effective for individuals who do not respond to UDCA (Corpechot et al., 2018; Honda et al., 2019; Iwasaki et al., 1999). Recent studies have shown fibrates to improve liver biochemistries and liver stiffness, in addition to increasing survival without liver transplantation (Corpechot et al., 2018; Honda et al., 2019).

Investigators have evaluated a number of other drugs, but none were effective as single agents, and those investigated in combination with UDCA did not yield greater benefit than UDCA alone (Lindor et al., 2019). More recently, researchers have been studying peroxisome proliferator activated receptor-alpha (PPAR- $\alpha$ ) agonists and various antifibrotic agents as potential PBC therapies (Gerussi et al., 2020).

### Animal Models

Investigators have developed a variety of animal models that recapitulate at least some of the clinical, histological, and immunological features of PBC. These models include genetically modified spontaneous models, xenobiotic immunized models, and infection-triggered models. No single animal model, however, reflects the varied clinical course and complex immunology of PBC (Katsumi et al., 2015).

### Research Progress and Gaps

The lack of effective medical therapies for treating PBC, and particularly for treating severe cases of itching skin in some individuals with PBC, represents a critical gap. Novel therapies continue to be investigated. Better genetic and immunology screening tests are needed to determine who is at elevated risk for developing PBC. Research on approaches to preventing histopathologic disease in those with positive serology is also required. New animal models that reflect the varied clinical course and complex immunology of PBC would be helpful. In addition, life-course studies that follow the patient through diagnosis, treatment, and disease sequelae, as well as incidence and prevalence studies that reflect the entire U.S. population, are needed.

## MULTIPLE SCLEROSIS

Multiple sclerosis is an autoimmune disorder of the CNS that causes inflammation that damages the myelin sheath enveloping the axons of neurons. This inflammation can also eventually affect the nerve fibers themselves, causing them to degenerate. Demyelination, with or without nerve fiber degeneration, interrupts transmission of signals that control muscle function and bring sensation from organs and limbs in the body (Mayo Clinic, 2020a; Podbielska et al., 2013). Depending on the location of the damage in the brain and spinal cord, a wide range of neurologic symptoms and impairment can occur, including vision problems, numbness, tremor, lack of coordination, impaired balance, weakness, bowel and bladder problems, and inability to walk (Mayo Clinic, 2021c). In addition, fatigue is a common manifestation of multiple sclerosis and has been found to have a significant negative impact on patient-reported quality of life (Young et al., 2021).

Relapsing-remitting multiple sclerosis is the type of multiple sclerosis initially diagnosed among 85 percent of individuals with a new diagnosis of multiple sclerosis; it is characterized by episodes of neurological relapses followed by partial or complete neurologic recovery

(Goldenberg, 2012). In a majority of individuals, symptoms remit over a period of weeks to months. Prior to the development of disease-modifying therapies, about half of individuals with relapsing-remitting multiple sclerosis would transition to a second phase, called secondary progressive multiple sclerosis, within 10 years (National Multiple Sclerosis Society, n.d.-a). The course of secondary progressive multiple sclerosis is characterized by neurologic progression, with few or no episodes of relapse.

Primary progressive multiple sclerosis is a different type of multiple sclerosis, and it is initially diagnosed in 15 percent of individuals with a new diagnosis. It is characterized by neurological progression from the onset of presentation, without relapses and remissions early in the course of disease (National Multiple Sclerosis Society, n.d.-b, 2020; Thompson et al., 2018).

### Epidemiology and Impact

Information on disparities in the epidemiology of multiple sclerosis can be found in Box 3-9.

#### BOX 3-9

#### Multiple Sclerosis: Sex, Age, Racial, and Ethnic Disparities

- Prevalence is 2.8 times higher in women than men (Wallin et al., 2019)
  - Nearly equal proportions of men and women have primary progressive multiple sclerosis
- Typical onset of primary progressive multiple sclerosis is 10 years later than for relapsing-remitting multiple sclerosis (Tremlett et al., 2005, Table 2, p. 1921)
- Mean age for clinical diagnosis of adult-onset disease is 30 years (Mayo Clinic, 2021c)
  - Childhood onset is rare, occurring in 2–10 percent of cases (Yan et al., 2020; Yeh et al., 2009)
- Incidence in Black individual, 10.2 per 100,000 person-years; White individuals, 6.9 per 100,000 person-years; Hispanic individuals, 2.9 per 100,000 person-years; Asian and Pacific Islander individuals, 1.4 per 100,000 person-years (Langer-Gould et al., 2013)
- Prevalence is higher in non-Hispanic Black compared with non-Hispanic White populations, with lower prevalence in Asian, Pacific Islander, and Hispanic populations (Romanelli et al., 2020)

### *Complications, Other Morbidity, and Long-Term Consequences*

There is significant clinical heterogeneity in multiple sclerosis, with a varied accumulation of disability. The disease is a major cause of disability in young adults, particularly if it enters a progressive phase with persistent, non-remitting neurologic manifestations (Dimitrov and Turner, 2014). There are also substantial financial and psychosocial costs to the individual and society (Rodriguez-Rincon et al., 2019; Schriefer et al., 2021).

Complications that commonly accompany multiple sclerosis include urinary tract infections from bladder dysfunction and pressure ulcers resulting from immobility. Research has yet to determine whether depression is a primary manifestation, a complication of multiple sclerosis, or both. The lifetime risk of depression among those with multiple sclerosis is estimated to reach as high as 50 percent (Sadovnick et al., 1996), and the prevalence of depression is estimated to be 26 percent in the 18- to 45-year-old subgroup of those with multiple sclerosis (Patten et al., 2003). The occurrence of moderate to severe depressive symptoms in individuals with multiple sclerosis is approximately double that of age-matched individuals in the general population (Chan et al., 2021). Anxiety and sleep disorders—with or without memory problems—also appear to be more common in individuals with multiple sclerosis than in the general population (Bamer et al., 2008; Boeschoten et al., 2017; Hughes et al., 2018; Sumowski et al., 2021).

Other disorders that studies have found to have a higher prevalence in individuals with multiple sclerosis relative to populations without multiple sclerosis include hypertension, hypercholesterolemia, and chronic lung disease, though research has not identified the mechanisms for these associations (Magyari and Sorensen, 2020; Narula, 2016). Research has also shown that autoimmune disorders including type 1 diabetes, psoriasis, and IBD have a higher prevalence in persons with multiple sclerosis than in persons without the disease (Magyari and Sorensen, 2020).

### *Economic Impact*

A 2013 review of studies examining the health care costs of multiple sclerosis noted that the estimated annual direct costs per patient of \$21,238 in 2011 dollars were second only to congestive heart failure (Adelman et al., 2013). The studies cited in the review were conducted between 1999 and 2008 and so would not have included costs of newer, more expensive drug therapies.

## Risk Factors and Etiology

The cause of multiple sclerosis is not known, though research has identified a number of genetic and environmental factors that increase the risk of developing multiple sclerosis. Much of the evidence suggests that multiple sclerosis results when one or more environmental factors interact with a genetic predisposition to the disease. The risk of developing multiple sclerosis is up to 20 percent higher for individuals with a parent or sibling with multiple sclerosis compared with those with no family history of the disease (Compston and Coles, 2002, 2008), which suggests the influence of both genetic and environmental factors. The main marker of genetic susceptibility to the disease is located in the HLA coding region of the human genome, although research has identified more than 200 other loci affecting risk (Canto and Oksenberg, 2018). In addition to the genetic risk, epidemiological studies have identified numerous environmental risk factors for the development and/or progression of multiple sclerosis, including exposure to EBV (Biström et al., 2021; Langer-Gould et al., 2017), early-life obesity, vitamin D deficiency, cigarette smoking, and exposure to air pollution (Aa Høglund et al., 2021; Ascherio and Munger, 2016; Huppke et al., 2019; Munger et al., 2016; Noorimotagh et al., 2021). A recent study of more than 10 million active-duty U.S. personnel between 1993 and 2003 found that risk of developing multiple sclerosis increased 32-fold after infection with EBV (Bjornevik et al., 2022). Exposure to early-life obesity, smoking, or EBV appear to interact with an HLA risk allele to result in an even higher risk of multiple sclerosis, although the biological explanations for these gene-environment interactions are far from clear (Hedström et al., 2021; Olsson et al., 2017). Increasingly, research is showing that the gut microbiome is a potential factor in the development of multiple sclerosis (Burton, 2018).

## Diagnostic Tools

There is no single feature or diagnostic test for multiple sclerosis. Rather, clinicians make a diagnosis of multiple sclerosis based on a combination of historical and physical examination, and imaging findings. Diagnostic criteria proposed in 1965 and 1983 called for a multiple sclerosis diagnosis based on two separate attacks of neurologic symptoms, including motor, sensory, or visual disturbances, that are disseminated in terms of the location of CNS lesions and occur at least 1 month apart, excluding other diseases with similar features (Poser et al., 1983; Schumacher et al., 1965). The 1983 guidelines aimed to establish more objective and standardized diagnostic criteria, as well as supporting laboratory features including presence of increased IgG levels in the cerebrospinal fluid but normal levels in serum (Poser et al., 1983).

Newer diagnostic criteria proposed in 2001, 2005, and 2010 incorporate brain MRI criteria for establishing dissemination of CNS lesions in space and time (Polman et al., 2011). Brain MRI is the most sensitive test to estimate CNS lesion load and disease activity, progression, and prognosis. More recent criteria proposed in 2010 and 2017 enable a diagnosis from a single baseline MRI, which has the potential to result in earlier and more accurate diagnosis and lead to prompt treatment (Milo and Miller, 2014; van der Vuurst de Vries et al., 2018). Despite these advances, it remains challenging to diagnose multiple sclerosis because early symptoms can be vague and transient. In addition, there is no specific biomarker or laboratory test for multiple sclerosis (Solomon et al., 2019), and misdiagnosis can occur when the symptoms mimic those of other disease and healthy states (Calabrese et al., 2021).

There is increasing evidence that there are early signs of symptoms of multiple sclerosis that appear before the first overt symptoms appear (Giovannoni, 2017). MRI studies have detected asymptomatic lesions, especially during the early course of disease. In fact, MRI scans of asymptomatic first-degree relatives of people with multiple sclerosis find brain lesions in approximately 10 percent of those individuals. These lesions could indicate demyelination is occurring. Because these lesions fulfill the requirement to be disseminated in the CNS, this finding suggests there may be an asymptomatic preclinical state (De Stefano et al., 2006; Xia et al., 2017). In addition, clinically isolated syndrome refers to a single episode of neurologic symptoms lasting at least 24 hours and meeting other criteria that rules out other causes of the symptoms. If neuroimaging studies show abnormalities consistent with demyelination in the region that correlates with the neurologic symptoms, there is a 60–80 percent risk of developing multiple sclerosis within the next few years; when neuroimaging abnormalities are not present, there is a much lower (~20 percent) chance of developing multiple sclerosis over a similar time frame (National Multiple Sclerosis Society, n.d.-a). Initiation of disease-modifying therapy is often recommended, particularly for the high-risk category of clinically isolated syndrome (Jokubaitis et al., 2015a; National Multiple Sclerosis Society, n.d.-d; Tsivgoulis et al., 2015).

### Treatment and Prospects for Cures

FDA approved the first disease-modifying therapy for multiple sclerosis in the United States in 1993 (Loma and Heyman, 2011). Since then, FDA has approved a host of other agents that can be administered by pill, injection, or infusion (National Multiple Sclerosis Society, n.d.-c). These disease-modifying therapies target various aspects of the immune system to reduce the CNS inflammation that occurs in multiple sclerosis.

Disease-modifying therapies are generally most effective in those who have relapsing-remitting disease, have more active disease (as detected by MRI), who are younger, and who are less disabled (National Multiple Sclerosis Society, n.d.-b, 2020; Signori et al., 2015), with treatment delays associated with more clinical symptoms and more abnormalities in MRI scans (Comi, 2013; Deangelis and Miller, 2014; Jokubaitis et al., 2015b; Kavaliunas et al., 2017; Kinkel et al., 2006). To date, FDA has approved only one medication, ocrelizumab, for primary progressive multiple sclerosis (FDA, 2017a).

The National Multiple Sclerosis Society<sup>7</sup> website provides an overview of disease-modifying therapies for multiple sclerosis. A subgroup of disease-modifying therapies is characterized as “high-efficacy” or “highly effective” as they are more potent, but they usually also have a higher risk of serious side effects (Merkel et al., 2017). A thorough discussion of pros and cons is recommended for shared decision-making with patients (Col et al., 2019). Several international studies suggest that the advent of disease-modifying therapies has altered the natural history of relapsing-remitting multiple sclerosis (Beiki et al., 2019; Simonsen et al., 2021). Autologous hematopoietic stem-cell transplant (also known as bone marrow transplant) has been recommended as having sufficient evidence to be carefully considered for the minority of patients with multiple sclerosis whose disease activity is substantial and continues despite treatment with even a high-efficacy disease-modifying therapy, or for patients for whom there is a contraindication to a disease-modifying therapy. Owing to the serious risks that accompany this treatment, the National Multiple Sclerosis Society’s National Medical Advisory Committee recommends that candidates under the age of 50 and with disease of less than 10 years’ duration may have a better risk/benefit ratio for this aggressive treatment (Miller et al., 2021). As noted previously, fatigue is a symptom that significantly adversely affects many with multiple sclerosis. There is evidence that some behavioral and exercise interventions directed at reducing fatigue and its impact can be beneficial (Moss-Morris et al., 2021). With an estimated lifetime risk of depression in multiple sclerosis reaching as high as 50 percent, periodic screening and assessment, and implementation of treatment, is recommended (Patten, 2020; Skokou et al., 2012). Spasticity, balance and gait, and impairment in functional status are ideally addressed with rehabilitation and other modalities (Donzé and Massot, 2021).

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<sup>7</sup> Available at <https://www.nationalmssociety.org/Treating-MS/Medications#section-2> (accessed December 29, 2021).

## Animal Models

Investigators have developed several animal models to study aspects of the pathogenic mechanisms driving autoimmunity directed against the CNS (Procaccini et al., 2015). The most commonly studied is the experimental autoimmune encephalomyelitis (EAE) mouse model, in which immunizing the mice with specific proteins or peptides targeted by the immune system in multiple sclerosis induces an autoimmune demyelinating disease (Constantinescu et al., 2011). The specific features of disease that develop depend on the antigen used and the genetic strain of mouse, with some developing chronic CNS inflammation and others developing a relapsing-remitting course. This variability enables researchers to study the different disease courses seen in humans and has provided information regarding the autoimmune response, but the need to induce disease with immunization yields a more artificial model than in spontaneous models of the disease. Identification of specific peptides targeted by autoreactive T cells in EAE mouse model studies has led researchers to develop mice that they genetically engineer to express the pathogenic T-cell receptors, which results in an overabundance of pathogenic T cells that target the self-antigen and the spontaneous development of EAE (Frausto et al., 2007; Goverman, 2009).

In addition to EAE, researchers have developed procedures for inducing rodents to develop a demyelinating disease following infection with certain viruses, such as Theiler's murine encephalomyelitis virus or treatment with certain toxins (Gerhauser et al., 2019). Together, these models have enabled detailed studies of immune and non-immune features of demyelinating disease, including visualizing the interactions between cells within the brain and spinal cord, which is not as easily performed or studied in humans.

## Research Progress and Gaps

Regarding pathophysiology and identifying targets for treatment of multiple sclerosis, ongoing research includes investigating the role of the gut microbiome as well as the pathways by which inflammatory cells breach the barriers into the CNS. Genetic studies are investigating complex gene–environment interactions (Horng et al., 2017; Takewaki and Yamamura, 2021). While there has been substantial progress in using disease-modifying therapies to treat relapsing-remitting multiple sclerosis, there is currently limited evidence for therapies that slow progression in the progressive type of the disease. Given the greater prevalence of multiple sclerosis among women of child-bearing years, and the welcome advent of disease-modifying therapies, research to generate evidence on

the optimal management of multiple sclerosis before, during, and after pregnancy is needed. While there have been animal studies that have yielded targets for CNS remyelination, there are barriers to translating this knowledge to develop remyelination therapies, such as how to best design and best evaluate clinical trials (Lubetzki et al., 2020). The association of low vitamin D with disease onset and relapse frequency warrants further investigation of whether intervention to raise vitamin D levels can affect disease course (Mansoor et al., 2021). The roles of stem-cell transplantation and other cell therapies are not fully developed.

There is a substantial need to develop early-detection techniques to enable treatment to begin as early as possible. Early biomarkers, such as autoantibody screens and additional MRI indicators, are needed to detect disease sooner, before irreversible damage occurs. Early biomarkers would be particularly valuable for screening higher-risk, asymptomatic family members of people with multiple sclerosis who are more likely to have early subclinical manifestations of the disease. Developing early markers would benefit from cohort studies that follow high-risk individuals longitudinally. Prospective, longitudinal studies would also enable the study of multiple sclerosis from a life-course perspective. While several registries have been developed around the world in recent decades, one review found “a significant number of largely uncoordinated parallel studies,” and many of them use convenience samples (Bebo et al., 2018). From a public health perspective, there is a need to develop systems by which researchers can obtain reliable epidemiological data regarding the prevalence, incidence, and time trends of multiple sclerosis.

In addition, there is a need for health-services research to investigate and design interventions to overcome delays in the diagnosis of multiple sclerosis, including delays that differentially affect non-White persons and women, as well as those with decreased access to health care. Risk-stratification and prediction algorithms are needed to predict who is likely to have a more aggressive disease course as a means of guiding decision-making around the selection and sequence of use of disease-modifying therapies and other emerging therapies.

Treatments to manage the “invisible” symptoms of multiple sclerosis that have profound impacts on health-related quality of life, including fatigue, depression, and anxiety, lack a body of evidence, despite many promising leads (Lakin et al., 2021). The potential value of Chronic Care Model-based approaches in providing comprehensive multiple sclerosis care and implementing strategies to optimize care and patient outcomes is understudied, yet as the United States moves toward value-based payment models, such research evidence is needed to guide implementation of coordinated chronic care that will maximize patient outcomes (Cotton et al., 2016).

## TYPE 1 DIABETES

Type 1 diabetes is characterized by autoimmune damage, impairment, and eventual destruction of the insulin-producing pancreatic beta cells, which leads to a dependence on administered insulin. If not treated with insulin, type 1 diabetes leads to hyperglycemia, which, if unchecked, results in deadly diabetic ketoacidosis and coma in an acute state, and microvascular and macrovascular end-organ complications in a chronic state. Type 1 diabetes is generally preceded by the appearance of islet autoantibodies in the blood, defined as islet autoimmunity; however, not all those who develop islet autoimmunity progress to type 1 diabetes (Kwon et al., 2022; Regnell and Lernmark, 2017).

### Epidemiology and Impact

Information on disparities in the epidemiology of type 1 diabetes can be found in Box 3-10.

#### **BOX 3-10** **Type 1 Diabetes: Sex, Age, Racial, and Ethnic Disparities**

- Annual incidence in individuals 19 years and younger is almost twice that of adults 20–64 years of age (Rogers et al., 2017)
  - Disease occurrence peaks at ages 5–7 and again during puberty (Atkinson et al., 2014)
  - Incidence in the 0–19 age group increased 1.4 percent annually between 2002 and 2011 from 19.5 cases per 100,000 youths per year to 21.7 cases per 100,000 youths per year (Mayer-Davis et al., 2017)
  - Incidence increased 4.2 percent annually among Hispanic individuals ages 0–19 compared to 1.2 percent annually among non-Hispanic White individuals (Mayer-Davis et al., 2017)
- Males and females 19 years and younger have similar prevalence (Dabelea et al., 2014), though incidence increased between 2002 and 2012 in boys but not girls (Mayer-Davis et al., 2017)
  - Prevalence among all individuals 19 years and younger increased from 1.29 per 1,000 individuals in 2002 to 2.34 per 1,000 individuals in 2016 (Chen et al., 2019); this trend was not seen in a 1994–2010 study in Olmsted County, Minnesota (Cartee et al., 2016)
  - U.S. prevalence in the 0–19 age group is highest in non-Hispanic White populations compared to Hispanic, African-American, American Indian, and Native Alaskan populations (Dabelea et al., 2014)
- Adult males have a higher incidence of type 1 diabetes compared to females (Rogers et al., 2017)

*Complications, Other Morbidity, and Long-Term Consequences*

Diabetic ketoacidosis and severe hypoglycemia are acute and potentially life-threatening complications of type 1 diabetes. While type 1 diabetes is more common in non-Hispanic White people, the frequency of diabetic ketoacidosis is higher among ethnic minority individuals with lower socioeconomic status, and those who lack private health insurance (Rewers, 2018). The percentage of hospitalizations for severe hypoglycemia is higher in males compared with females and lower in White persons than in any other racial or ethnic group (Rewers, 2018). The chronic complications of type 1 diabetes include microvascular and macrovascular conditions. Individuals with type 1 diabetes are at increased risk for retinopathy leading to sight-loss/blindness (Klein and Klein, 2018), nephropathy leading to ESRD (Pavkov et al., 2018), and neuropathy and peripheral vascular disease leading to amputation (Boyko et al., 2018).

Individuals with type 1 diabetes are at increased risk of conditions such as heart disease and stroke (Barrett-Connor et al., 2018; Mayo Clinic, 2020b), as well as co-occurring autoimmune illnesses, particularly celiac disease (Cohn et al., 2014). A recent large study in Finland found that one out of five persons with type 1 diabetes develops one or more additional autoimmune diseases, with Graves' disease, Hashimoto's thyroiditis, and celiac disease being among the most common (Barker, 2006; Makimattila et al., 2020). The prevalence of depression is significantly higher in individuals with type 1 diabetes compared with those without diabetes (Farooqi et al., 2021). Eating disorders are twice as common in adolescent females with type 1 diabetes compared with those without diabetes, though few studies on this topic are available (Jones et al., 2000).

Individuals with type 1 diabetes are more likely to develop infections, such as bone and joint infections (Schwartz, 2018), acute cholecystitis, gastrointestinal infections, mycoses, pneumonia, sepsis, surgical site infections, endocarditis, meningitis, urinary tract infections, cellulitis, lower extremity infections and foot ulcers, and tuberculosis compared with individuals without type 1 diabetes (Carey et al., 2018; NIDDK, 2018a). Data consistently show that diabetes increases risk of severe COVID-19 (Hartmann-Boyce et al., 2021), although most studies did not distinguish between type 1 and type 2 diabetes. One population study in the United Kingdom found that the risk of in-hospital COVID-19-related death was markedly higher in people with type 1 diabetes compared with those with type 2 diabetes (Barron et al., 2020; Holman et al., 2020).

Type 1 diabetes increases the risk of mortality, stroke and cerebrovascular complications, myocardial infarction, and pre-eclampsia in pregnant individuals (NIDDK, 2018a). Women with type 1 diabetes have a higher risk of having infants with macrosomia and associated birth trauma, respiratory distress, and congenital malformations compared

with women without type 1 diabetes. The risks of poor outcomes in the mother and newborn are mitigated with better glycemic control during pregnancy although this requires intensive care and monitoring (Alexopoulos et al., 2019; Lemaitre et al., 2021; NIDDK, 2018a).

### *Economic Impact*

Individuals with type 1 diabetes incur, on average, \$1,981 more per year in medical costs than those without type 1 diabetes. The expected lifetime medical costs for all people with type 1 diabetes exceeds \$130 billion (Tao et al., 2010).

## **Risk Factors and Etiology**

In type 1 diabetes, the body's immune system mistakenly destroys the insulin-producing islet cells in the pancreas, leading to hypoglycemia and clinical diabetes. Type 1 diabetes is characterized by the presence of autoantibodies years prior to the diagnosis of the disease, making them strong serologic markers of preclinical disease. The autoantibodies that precede type 1 diabetes include antibodies to insulin, glutamic acid decarboxylase, islet antigen 2, and zinc transporter family member 8 antigens (Pietropaolo et al., 2012). While development of islet autoimmunity is highly predictive of future type 1 diabetes, not all those who develop islet autoimmunity progress to disease (Regnell and Lernmark, 2017). It is unknown what factors trigger this autoimmune attack and whether similar or different factors perpetuate the autoimmunity that eventually results in disease.

Genetics play a key role in type 1 diabetes etiology, with the strongest risk alleles mapped to the HLA region of the genome. Large-scale studies show that type 1 diabetes is a polygenic disease with more than 40 risk loci (Barrett et al., 2009). However, the incidence of type 1 diabetes has been increasing at an exponential rate (Onkamo et al., 1999), a change that is too rapid to be explained by genetic factors alone, which suggests a role for non-genetic factors in disease etiology (Norris et al., 2020).

While researchers have investigated several candidate environmental factors, they have yet to fully elucidate what role they play in the development of type 1 diabetes. Of these candidate environmental factors, a large number are related to *in utero* or neonatal exposures, including higher maternal age at delivery, higher maternal pre- or early-gestational obesity, maternal virus infections, and Cesarean section (Norris et al., 2020; Yue et al., 2018). However, given the relatively low incidence of the disease, it is difficult and costly to obtain data to investigate these factors. Researchers are also examining exposures during infancy, including increased infant

growth, shorter duration of breastfeeding, and timing of the introduction of solid foods, and omega-3 fatty acid intake and status (Norris et al., 2020). Research has provided some evidence that childhood exposures, such as higher cow's milk intake, higher gluten intake, higher sugar intake, lower vitamin D status, and enterovirus infection, are candidate risk factors for type 1 diabetes (Norris et al., 2020).

### Diagnostic Tools

It is possible to diagnose a clinical state of type 1 diabetes using an elevated 2-hour glucose measure during an oral glucose tolerance test, a high hemoglobin A1C blood test, two high random blood-sugar tests coupled with any of the signs and symptoms of diabetes, or two high fasting blood-sugar tests.

There are three distinct stages of type 1 diabetes (Insel et al., 2015). Stage 1 is defined by the presence of two or more diabetes-related autoantibodies in the blood with normal blood glucose levels (Insel et al., 2015). Stage 2 commences when blood glucose levels begin to rise, signaling functional impairment of the islet cells. Stage 3 occurs when symptoms of glucose dysregulation, such as the production of abnormally large volumes of dilute urine or diabetic ketoacidosis, appear. While a clinical diagnosis is made only at Stage 3, the likelihood of progressing from Stage 1 to Stage 3 is very high, with a 5- and 10-year risk of 44 percent and 70 percent, respectively (Insel et al., 2015; Ziegler et al., 2013; Zuily et al., 2015).

### Treatment and Prospects for Cures

Treatment for type 1 diabetes includes insulin therapy; dietary carbohydrate, fat, and protein counting; and frequent blood-sugar monitoring. The goal of treatment is to keep blood-sugar level as close to normal as possible and delay or prevent complications. Insulin therapy involves either multiple daily insulin injections or use of an insulin pump, a device worn outside of the body that dispenses insulin as needed. In 2019, FDA approved the "artificial pancreas," an implanted closed-loop insulin delivery device, for individuals with type 1 diabetes (FDA, 2018a, 2019). A Phase III clinical trial of pancreatic islet transplantation in persons with type 1 diabetes who have impaired awareness of hypoglycemia and are at elevated risk of severe hypoglycemic events showed improvement in blood glucose awareness and control (Hering et al., 2016) as well as quality of life (Foster et al., 2018). Studies have demonstrated that people who maintain tight blood glucose control in the early stages of disease are less likely to undergo retinopathy eye surgeries (DCCT/EDIC Research Group

et al., 2015) and are likely to live longer compared with those who do not (Writing Group for the DCCT/EDIC Research Group et al., 2015).

In studies of infants at risk for type 1 diabetes, one diet-manipulation study that replaced cow's milk-based infant formula with hydrolyzed infant formula had no effect on the incidence of islet autoantibodies (Knip et al., 2014) or diabetes (Writing Group for the TRIGR Study Group et al., 2018), while another study that removed bovine insulin from infant formula showed a decrease in incidence of islet autoimmunity at 3 years of age (Vaarala et al., 2012). A third study found that delaying gluten exposure until age 12 months did not substantially reduce the risk of islet autoimmunity (Hummel et al., 2011). Interventions targeting the immune system have not slowed, halted, or reversed the destruction of insulin-producing beta cells (Skyler et al., 2018). Only one of nine secondary prevention trials—a trial of the anti-CD3 antibody teplizumab (Herold et al., 2019)—showed any delay in progression of individuals with Stage 1 or Stage 2 disease to full-blown type 1 diabetes (Diabetes Prevention Trial—Type 1 Diabetes Study Group, 2002; Elding Larsson et al., 2018; Gale et al., 2004; Krischer et al., 2017; Lampeter et al., 1998; Näntö-Salonen et al., 2008; Vandemeulebroucke et al., 2009; Vehik et al., 2011).

### Animal Models

Three spontaneous autoimmune animal models, including the non-obese diabetic mouse, the biobreeding Komeda rat, and the LEW.1AR1-*iddm* rat, are the primary animal models for studying type 1 diabetes (Al-Awar et al., 2016; King, 2012; Kottaisamy et al., 2021). These models allow the researcher to examine beta cell destruction during an autoimmune process, probe the genetics and mechanisms underlying type 1 diabetes, manipulate the autoimmune process, and study treatments that prevent beta cell death. Genetically induced models include the AKITA mouse and the KINGS  $\text{Ins}2^{+/G32S}$  mouse, which demonstrate beta cell destruction resulting from endoplasmic reticulum stress (King, 2012). Researchers can use them as transplantation models and to develop new insulin formulations and treatments to prevent endoplasmic reticulum stress. Virally induced animal models enable researchers to investigate beta cell destruction induced by viral infection of the beta cells, while chemically induced models are useful as transplantation models and for investigating new formulations of insulin and treatments that may prevent beta cell death (King, 2012).

## Research Progress and Gaps

Medical science has made great strides in treating type 1 diabetes and preventing its complications. The nation has built a critical research infrastructure to investigate the prevention of type 1 diabetes, including clinical trial networks such as TrialNet and the Immune Tolerance Network. While there have been a number of clinical trials, only one has been successful to date in delaying progression to type 1 diabetes. Other research infrastructure includes large natural history studies, such as TEDDY, DAISY, Germany's BABYDIAB study,<sup>8</sup> and the Type 1 Diabetes Prediction and Prevention Study,<sup>9</sup> many of which NIH funds. These large birth cohort studies have enabled researchers to investigate the life course of type 1 diabetes, providing important clues as to the appropriate timing and approaches for prevention. The Type 1 Diabetes Genetics Consortium has thoroughly explored the genetics of type 1 diabetes. The SEARCH for Diabetes in Youth study and other population-based registries, such as the Colorado and Pittsburgh Insulin-Dependent Diabetes Mellitus registries, have enabled researchers to determine the incidence and prevalence of type 1 diabetes in the United States.

Technology advances are greatly simplifying the effort required by patients of all ages to monitor and control their blood glucose levels. In addition, pancreatic islet transplantation has shown benefit in patients with hard-to-control blood glucose levels who are at elevated risk of hypoglycemic events (NIDDK, 2018b).

Despite this infrastructure and progress, there remain gaps in knowledge about type 1 diabetes. The planned termination of TEDDY, in 2025 (Clinicaltrials.gov, 2006) illustrates a concern about ending valuable studies prematurely. This observation study, which has focused on the development of autoimmune diseases in newborns at risk of developing type 1 diabetes (NIDDK, 2021b), has gathered valuable data and samples. However, with a follow-up of only 15 years, many participants who are likely to develop disease will be disenrolled before clinical diagnosis, and disease-associated autoantibodies will not be tracked long enough to discern natural evolution or clinical outcomes.

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<sup>8</sup> The German BABYDIAB study was a prospective German multicenter study that monitored 1,353 offspring of parents with type 1 diabetes (Ziegler et al., 1999). Children were monitored at birth, 9 months, and 2, 5, and 8 years of age for the temporal development of autoantibodies.

<sup>9</sup> The DIPP Study is a Finnish prospective observational cohort study of infants born with a DR-DQ genotype associated with increased risk for type 1 diabetes (NLM, 2020). The families are invited to have examinations of the infant every 3 months for 2 years, and then every 12 months until age 15 or until diagnosis of type 1 diabetes.

Research to identify the exact environmental triggers (including whether or not environmental factors differentially influence risk in different racial and ethnic groups, and gene-environment interactions), and understand the role of the *in utero* environment, inflammation, and pancreatic beta cell stress in the etiology of type 1 diabetes is necessary. Additional investigation as to why some individuals develop autoimmunity but do not advance to type 1 diabetes may provide valuable information regarding how to stop the autoimmune process from progressing and thus prevent clinical disease. While it is estimated that half of all type 1 diabetes presents after the age of 18, there is a paucity of data on adult-onset type 1 diabetes.

## AUTOIMMUNE THYROID DISEASES

Autoimmune thyroid diseases are believed to be among the most common autoimmune diseases, and among them are Hashimoto's thyroiditis and Graves' disease, which are the leading causes of hypothyroidism and hyperthyroidism, respectively (Franco et al., 2013). In both of these diseases, autoantibodies attack the thyroid gland. In Hashimoto's thyroiditis, this autoantibody attack may have no effect on the thyroid initially, or it may cause the thyroid to be underactive, or rarely, overactive. In most individuals, however, the thyroid eventually becomes underactive, resulting in an enlargement of the thyroid and sometimes fatigue and decreased tolerance to cold (Hershman, 2020a). In Graves' disease, the thyroid is stimulated to produce and secrete excess thyroid hormones, which typically lead to an enlarged thyroid and increased bodily functions such as heart rate and blood pressure, which can yield excessive sweating, anxiety, weight loss, and difficulty sleeping (Hershman, 2020b). Graves' disease can also affect the eyes, causing symptoms such as tearing, redness, pain, vision problems, and bulging eyes (Watson, 2021).

### Epidemiology and Impact

Information on disparities in the epidemiology of autoimmune thyroid disease can be found in Box 3-11.

**BOX 3-11**  
**Autoimmune Thyroid Disease: Sex, Age,  
Racial, and Ethnic Disparities**

- Up to 95 percent of cases occur in females, with onset typically in mid-to-late adulthood (Cooper and Stroehla, 2003); epidemiologic data are lacking for males because of its scarcity in males
- Prevalence of Hashimoto's thyroiditis is highest in White females compared with Black females (Masi, 1965; McLeod et al., 2014)
  - Prevalence of anti-thyroid antibodies was highest among White populations, followed by Mexican American populations, and was lowest in Black populations (Hollowell et al., 2002)
- Incidence of Graves' disease among active duty military personnel was significantly higher among individuals from Black and Asian or Pacific Islander populations compared with those from White populations, and trended higher in Hispanic populations compared with White populations (McLeod et al., 2014)

#### *Complications, Other Morbidity, and Long-Term Consequences*

A number of risks are associated with hypo- or hyper-thyroidism that occurs for prolonged periods, even if the disease is subclinical or asymptomatic, such as from undiagnosed thyroid disease or under- or overtreatment. Risks include elevated mortality, dementia, cardiovascular diseases, and osteoporosis (Abrahamsen et al., 2014; Lillevang-Johansen et al., 2017, 2018, 2019). Women may have an increased risk of infertility, miscarriage, and preterm delivery, and there may be adverse effects on neurodevelopment in their children (Galofre and Davies, 2009). Between 25 and 50 percent of individuals with Graves' disease develop Graves' orbitopathy, a condition that can cause eye inflammation, swelling, irritation, and pain as well as eyelid retraction and bulging eyes; it can be disfiguring and can endanger sight (MedlinePlus, 2020).

Hashimoto's thyroiditis is associated with an increased risk of thyroid cancer (Penta et al., 2018; Resende de Paiva et al., 2017) as is Graves' disease, particularly in persons with thyroid nodules (Chen et al., 2013; Staniforth et al., 2016). While findings are mixed regarding an increased risk of breast cancer in those with Graves' disease, it is recommended that these patients be monitored (Chen et al., 2013; Yang et al., 2020).

Persons with an autoimmune thyroid disease are at a greater risk of developing other autoimmune diseases than persons without an autoimmune thyroid disease. One cross-sectional study of more than 3,000 White UK patients with Graves' disease or Hashimoto's thyroiditis observed a relative risk greater than 10.0 of developing pernicious anemia, SLE,

Addison's disease (particularly in men with Hashimoto's thyroiditis), myasthenia gravis (in men with Graves' disease and women with Hashimoto's thyroiditis), celiac disease, vitiligo, and multiple sclerosis (in men with Hashimoto's thyroiditis) (Boelaert et al., 2010). Sjögren's disease is also highly associated with autoimmune thyroid diseases (Baldini et al., 2018; Rojas-Villarraga et al., 2012).

Individuals with Hashimoto's thyroiditis are at an increased risk of developing depression and anxiety disorders (Siegmann et al., 2018). Depression is common in Graves' disease (Fukao et al., 2020), and experiencing disfigurement increases emotional distress (Farid et al., 2005).

### *Economic Impact*

A study published in 2021 estimated that annual per patient medical costs related to hypothyroidism ranged from \$460 to \$2,555 (Hepp et al., 2021). However, this study was not restricted to autoimmune hypothyroidism and did not assess the economic costs of Graves' disease or Hashimoto's thyroiditis.

### **Risk Factors and Etiology**

A temporal increase in disease incidence over a relatively short time, such as that observed in the Rochester, Minnesota, population for autoimmune thyroid diseases, supports the hypothesis that environmental factors play a key role in the development of disease. Dietary factors are leading contenders among suspected risk factors. There is some evidence that in iodine-sufficient areas, excess iodine intake may be associated with development of hypothyroidism in susceptible individuals (Konno et al., 1994; Laurberg et al., 1998; Sundick et al., 1992). While iodine is essential for normal thyroid function, both deficient and excessive intake have been associated with autoimmune thyroid disease. Selenium deficiency is another dietary factor that has been linked to autoimmune thyroid disease, and studies of supplementation among persons with subclinical hypothyroidism have suggested reduction in markers of thyroid autoimmunity (Duntas et al., 2003; Gärtner et al., 2002).

Smoking is associated with autoimmune thyroid disease; a meta-analysis reported an odds ratio of 3.3 for Graves' disease in current smokers compared with non-smokers. (Vestergaard, 2002). Data suggest that smoking is particularly relevant to the development of Graves' ophthalmopathy (Hägg and Asplund, 1987; Prummel and Wiersinga, 1993). Studies have shown that a number of toxins, including polychlorinated biphenyls, phthalates, bisphenol A, and brominated flame retardants, may have thyroid-disrupting effects, but long-term epidemiologic data

assessing exposures over varying developmental stages, including *in utero*, are needed to determine whether these substances play any role in the development of autoimmune thyroid disease (Boas et al., 2012).

Investigators have also postulated that infectious agents play a role in the development of autoimmune thyroid diseases, with evidence accumulating in particular for hepatitis C (Deutsch et al., 1997) and its treatment with interferon- $\alpha$  (IFN $\alpha$ ). Clinical or subclinical thyroid disease develops in approximately 40 percent of patients with hepatitis C treated with IFN $\alpha$ . IFN $\alpha$ -induced thyroiditis is thought to result from both immune effects and direct toxicity on the thyroid, with both autoimmune and non-autoimmune thyroiditis observed in association with this therapy (Menconi et al., 2011).

Genetic susceptibility also plays a key role in both Hashimoto's thyroiditis and Graves' disease, with family studies demonstrating high sibling risk ratios and twin concordance (Tomer, 2014). Research has implicated both thyroid-specific genes such as those coding for thyroglobulin and thyroid-stimulating hormone receptor, and immune-regulatory genes. Hashimoto's thyroiditis and Graves' disease share most of the susceptibility genes, and several are also shared with other autoimmune diseases (Tomer, 2014). Most of the susceptibility genes identified from genome-wide association studies have low odds ratios (Chu et al., 2011; Cooper et al., 2012; Hodge and Greenberg, 2016), pointing to the importance of genomic interactions with environmental factors. Recent research supports the role of epigenetic modulation in the development of Hashimoto's thyroiditis and Graves' disease (Tomer, 2014).

### Diagnostic Tools

While symptoms of autoimmune thyroid disease are generally non-specific, such as weight change, changes in appetite, fatigue, and dry skin, diagnosis relies on objective laboratory testing for thyroid hormone, thyroid-stimulating hormone, and autoantibodies. The major autoantibodies include anti-thyroid peroxidase, anti-thyroglobulin, and anti-thyroid-stimulating hormone receptor antibodies (Frohlich and Wahl, 2017). These autoantibodies are highly prevalent among patients with autoimmune thyroid disease, but are not specific in that they can also be observed in persons without thyroid disease.

### Treatments and Prospects for Cures

Although clinical guidelines for autoimmune thyroid diseases have been updated, the standard therapies for autoimmune thyroid diseases have remained stagnant for several decades, are associated with serious

complications, and do not target underlying autoimmune processes (Yoo and Chung, 2016). Anti-thyroid medications, thyroid ablation with radioactive iodine, or surgery are treatments for Graves' hyperthyroidism. Potential toxicities of anti-thyroid medications include agranulocytosis, liver toxicity, and birth defects (Andersen et al., 2013; Cooper, 2005), and the use of these medications is largely limited to serving as a bridge therapy prior to radioiodine or thyroidectomy. Radioiodine can trigger or worsen Graves' ophthalmopathy, may increase risk of breast and other solid cancers (Kitahara et al., 2019), and is associated with pregnancy complications for up to 3 to 5 years after treatment. Risks associated with thyroidectomy include vocal cord paralysis and hypocalcemia. Thyroid hormone replacement is used following radioiodine therapy or thyroidectomy for Graves' disease as well as for treatment of Hashimoto's thyroiditis. However, inconsistent absorption and bioavailability create challenges in achieving appropriate levels, with over half of patients undergoing thyroid hormone replacement failing to have normal thyroid hormone levels (Somwaru et al., 2009). In addition, bioequivalence may vary between thyroxine products, such as between brands and generics, and since imprecise treatment can have adverse effects, it is important to switch brands with caution and to use appropriate monitoring (Benvenga and Carlé, 2019).

There is a great need for targeted therapies that address immunological aspects of autoimmune thyroid diseases and that have fewer side effects, and there have been promising advances in that regard. Teprotumumab, a monoclonal antibody that inhibits insulin-like growth factor-1 receptor, was originally investigated as a cancer treatment but received FDA approval in 2020 for treatment of Graves' ophthalmopathy (Kahaly et al., 2021; Slentz et al., 2020).

A novel anti-CD40 monoclonal antibody, iscalimab, is currently in clinical trials for treatment of Graves' disease (Kahaly et al., 2020). This therapy builds on several years of basic and translational research elucidating the role of CD40 in Graves' disease, as well as other autoimmune diseases (Jacobson et al., 2005; Tomer et al., 2002). Ongoing research is investigating a personalized medicine approach for this treatment that aims to determine whether response can be predicted based on genotype.

Another promising compound for treatment of autoimmune thyroid disease is cepharanthine, which is currently in preclinical studies (Li et al., 2016, 2020). This small molecule blocks binding of thyroglobulin peptide and presentation to T cells, providing a targeted immunosuppression. It also represents another therapy that may offer a personalized treatment approach, predicted to be relevant for a subset of approximately one-third of patients with autoimmune thyroid disease.

### Animal Models

Experimental autoimmune thyroiditis can be induced by immunization of genetically susceptible animals with human thyroglobulin in an adjuvant and has served as a model for Hashimoto's thyroiditis (Kong, 2007). Graves' hyperthyroidism can be induced by injecting cells expressing the thyroid-stimulating hormone receptor or by vaccinating with thyroid-stimulating hormone receptor-encoding DNA in plasmid or adenoviral vectors (McLachlan et al., 2005). More recently, researchers have used the NOD.H-2h4 mice, one of relatively few animal models to spontaneously develop organ-specific autoimmune diseases without immunization with antigen and adjuvant, as a model of autoimmune thyroiditis (Braley-Mullen and Yu, 2015).

### Research Progress and Gaps

FDA approval in 2020 of a monoclonal antibody for treatment of Graves' ophthalmopathy represented a major advance in this field, where the majority of treatments have remained unchanged over decades. Despite progress in understanding of molecular mechanisms driving autoimmune thyroid diseases, there remains a need to improve understanding of risk factors and disease mechanisms and to translate these findings into development or repurposing of targeted interventions for prevention or treatment. Improved characterization of biomarkers and their implications for diagnosis is also needed in order to personalize screening and treatment approaches. Given the challenges and complications related to both undiagnosed and treated autoimmune thyroid diseases during preconception and pregnancy, special consideration to reproductive issues should be integrated into research. Additionally, studies are needed to assess the economic costs and impact of Graves' disease and Hashimoto's thyroiditis.

### SUMMARY AND RESEARCH IMPLICATIONS

Sjögren's disease, SLE, APS, rheumatoid arthritis, psoriasis, IBD, celiac disease, PBC, multiple sclerosis, type 1 diabetes, and autoimmune thyroid diseases are well-studied representatives of organ-specific and systemic autoimmune diseases. These illnesses share genetic, cell-biology, and etiologic mechanisms in diverse ways that with further study could lead to identifying specific autoimmune mechanisms involved in these diseases. Several treatment interventions are shared among some autoimmune diseases.

Most of these autoimmune diseases are female predominant, though they differ in median age of onset and racial and ethnic distributions. For

several, however, epidemiological studies are inadequate or nonexistent. Such studies should be encouraged to fully understand the incidence and prevalence of these diseases and any racial-, ethnic-, or gender-related disparities. Like all autoimmune diseases, the diseases reviewed above are chronic illnesses; some are lethal, others are disabling, and some are neither. With regard to pregnancy, autoimmune diseases and their treatments may affect both mother and fetus. Treatment options vary, with some diseases lacking FDA-approved treatment options altogether. None is easy to treat. None has a known cure.

Autoimmune diseases are heterogeneous. For some, diagnostic testing is well-established and diagnosis relatively straightforward. For others, diagnostic markers may be nonspecific, and final diagnosis may depend on variable combinations of symptoms, signs, laboratory markers, responses to treatment, genetics, and environmental exposure studies. For this latter group of autoimmune diseases, it is imperative to identify more specific diagnostic markers, both for the purposes of diagnosing these diseases as early as possible and to support efforts to develop effective therapeutics.

Co-occurrence of autoimmune diseases in individual patients is common. Complications arising from disease-inflicted damage and/or from treatment, occurring over prolonged periods of time, may hinder identification of broadly applicable interventions. In addition, a lack of standards for recording diagnosis codes and metrics for assessing outcomes make it difficult to determine the cost of care, disability, and mortality.

Animal models provide insight into pathophysiologic mechanisms of autoimmune disease to varying degrees, though no animal model perfectly recapitulates human autoimmune disease. Still, basic mechanisms of immune function and immune dysregulation can be more easily studied in appropriate animal models for specific diseases to provide a more directed, hypothesis-driven study of disease mechanisms in humans. Thus the value of animal models should be appreciated, and studies that develop new animal models or advance existing models are encouraged.

Despite the ambiguities, understanding the genetics, involvement of environmental exposures, and pathogenic mechanisms of autoimmune diseases suggest possibilities for initiatives to prevent disease. The second-hit hypothesis—that individuals may be genetically predisposed to develop clinical illness but do not do so unless and until exposures or events occur—is a theme common to all autoimmune diseases and one that merits further study, including whether such exposures or events differentially influence risk in specific ethnic and racial populations.

There are barriers to studying autoimmune diseases when there are rigid classification criteria for enrolling individuals with an autoimmune

disease diagnosis in a study.<sup>10</sup> Among these are the prolonged time between autoimmunity onset and diagnosis, resulting from the absence of sensitive diagnostic biomarkers and clinician awareness of early disease manifestations; disease heterogeneity, including pre-diagnosis and in individuals who have overlapping autoimmune disease or who present atypically; and coexisting illnesses. Collaborative studies, using broad diagnostic criteria, provide opportunities to improve etiological, mechanistic, treatment, and outcome knowledge that could be applied to more patients and improve overall patient care.

Among the autoimmune diseases discussed in this chapter, no individual disease represents a full range of comprehensive studies or characterization. Sjögren's disease, for example, represents a complex autoimmune disease that targets common self-antigens, disproportionately affects women, and may affect individuals across the life course. But limiting epidemiological studies in Sjögren's disease to individuals with no co-occurring autoimmune disease has greatly hindered characterization of the full impact of Sjögren's disease. Other diseases have been better characterized through epidemiological studies, including SLE, rheumatoid arthritis, IBD, and type 1 diabetes. Studies have best examined economic impact for the gastrointestinal diseases IBD and PBC. Type 1 diabetes represents a model autoimmune disease in that extensive study has identified autoantibodies to predict disease development and to enable intervention studies in individuals at highest risk for developing autoimmunity. Ultimately, this represents a key goal in autoimmune disease research—defining highly at-risk individuals and intervening to prevent progression to disease. Together these autoimmune diseases represent successes and gaps in our understanding that can be considered in the future funding and coordination of autoimmune disease research.

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<sup>10</sup> Many systemic autoimmune diseases are predictable before they are diagnosable. For example, many patients who later develop SLE, type 1 diabetes, or PBC have blood test abnormalities—typically the presence of autoantibodies, which are sometimes associated with genetic markers—that antedate the onset of clinical illness by a decade. Similarly, a limited form of neurological illness known as clinically isolated syndrome may precede diagnosable multiple sclerosis. And nonspecific IBD may precede diagnosable Crohn's disease or ulcerative colitis. The predictive power of pre-disease is not high, since many pre-disease patients do not progress to diagnosable disease. In most cases, it is unknown whether the differences between pre-disease and diagnosable disease reflect disease severity or chronology of disease pathogenesis. Clinicians, scientists, and administrators disagree whether pre-disease patients should be included in studies and conversations about specific diagnoses.

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## Crosscutting Issues in Autoimmune Diseases

In Chapter 1 and Chapter 3, the committee highlighted unique and heterogeneous features of specific autoimmune diseases. In contrast, this chapter examines common features found among many autoimmune diseases. Because discussion applies to autoimmune diseases as a category of diseases, the 11 diseases of focus as well as other autoimmune diseases, such as alopecia areata, juvenile idiopathic arthritis, myocarditis, spondyloarthropathy, systemic sclerosis (also known as scleroderma), and vasculitis, are referenced.

### COMMONALITIES ACROSS AUTOIMMUNE DISEASES

While every autoimmune disease has its unique characteristics, many of them also share common features that researchers believe—and evidence supports—suggest that there are common mechanisms involved in the etiology of autoimmune diseases. For example, the fact that autoimmune diseases tend to occur in family clusters suggests that there are common genetic and environmental factors involved in triggering autoimmunity and disease symptoms. Research shows that genetic factors alone cannot explain the etiology of any autoimmune disease, and that environmental agents or insults—*infectious microorganisms and respiratory and dietary exposures* are leading candidates for several autoimmune diseases—are interacting with those genetic factors to produce the disease state. Certain types of proinflammatory immune responses and the presence of autoantibodies are two other common features. Finally,

multiple autoimmune diseases show sex differences in disease incidence and severity. The discussion below highlights how these commonalities, as well as common mechanistic pathways, can serve as therapeutic targets.

### Genetics

Research suggests strongly that autoimmunity leading to autoimmune disease requires at least one, but likely more than one, gene (Sogkas et al., 2021) that interacts with environmental factors. The gene–environment relationship is complex, with environmental changes altering genes through epigenetic modifications that not only affect that individual but subsequent offspring (Cavalli and Heard, 2019; Surace and Hedrich, 2019). Epigenetic factors could contribute to early onset of some autoimmune diseases such juvenile idiopathic arthritis (Meyer et al., 2015). Individuals with one autoimmune disease are more likely to develop another autoimmune disease (Cojocaru et al., 2010), and autoimmune diseases, although often not the same autoimmune disease, typically cluster in families (Shamim and Miller, 2000). In addition, autoantibodies are more likely to develop in family members, whether symptomatic or not, of an individual with an autoimmune disease (James et al., 2019; Leslie et al., 2001). These findings, along with the observation that autoimmune diseases run in families, lead the research community to believe that common mechanisms increase autoimmunity in genetically susceptible individuals.

Human leukocyte antigen (HLA), or HLA haplotype, is the best available predictor of developing an autoimmune disease (Bacon et al., 1974; Cooper et al., 1999; Matzaraki et al., 2017) and is directly related to increased autoantibodies in family members (Wong and Wen, 2003), though it does not appear to be the only region of the genome where different autoimmune diseases have genes in common (Cho and Gregersen, 2011; Cooper et al., 1999). Many of the genes that confer susceptibility to autoimmune disease and that different autoimmune diseases share regulate the immune response (Sogkas et al., 2021). Some autoimmune diseases with different clinical characteristics, including which organs are affected, share genetic variants, indicating that these diseases may share some common pathways of immune dysfunction (see Figure 4-1 and Figure 4-2). This supports the suggestion that the specific organs targeted in individuals with similar genetic risk variants, such as in families with multiple affected individuals, may require an additional factor such as an environmental exposure for disease to progress. In addition to the 11 diseases of focus, Figure 4-1 and Figure 4-2 include systemic sclerosis, spondyloarthropathy, primary sclerosing cholangitis, and juvenile

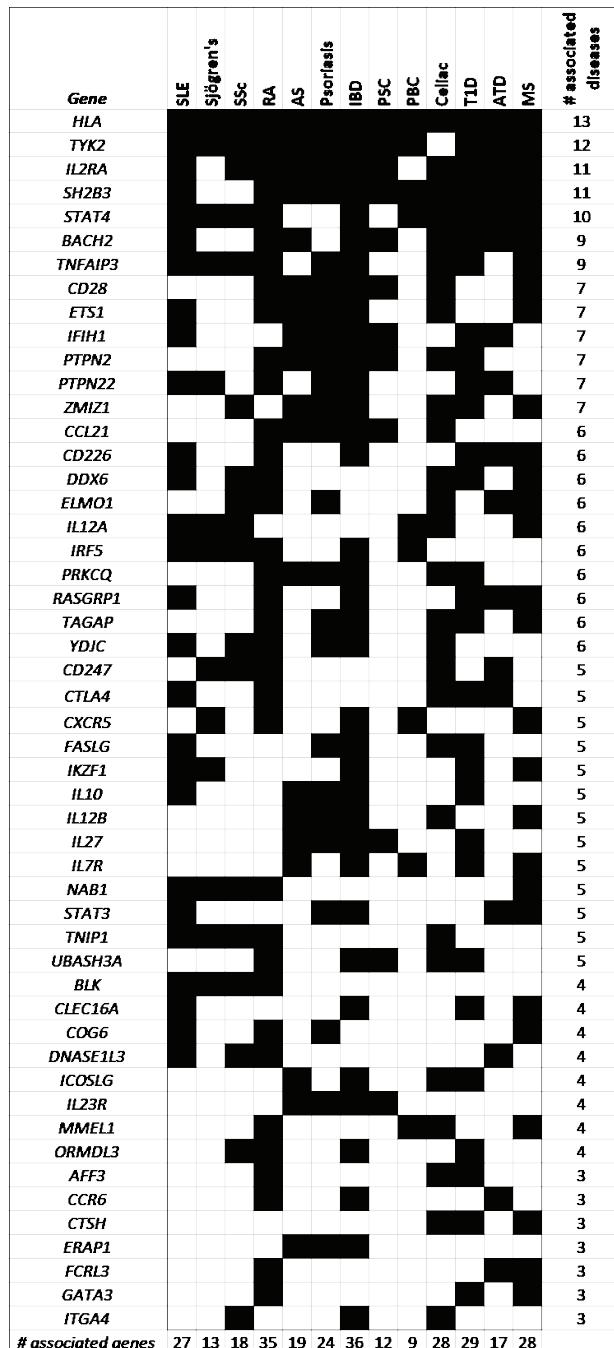


FIGURE 4-1 Shared genetic risk associations across autoimmune diseases.

continued

**FIGURE 4-1** Continued

NOTES: Variants associated with genes listed in the left column are associated with autoimmune diseases listed across the top as indicated by a filled black box. The column at the far right indicates how many autoimmune diseases in the table are associated with the gene. The bottom row indicates the number of genes in the table that are associated with the disease. This list is representative, showing genes with variants associated with multiple different autoimmune diseases. It is not a comprehensive list of all disease-associated genes, and it does not necessarily include all genes associated with each disease listed nor all diseases associated with each gene. Data were compiled through review of genome-wide association studies (GWAS) of the indicated diseases and associated references as well as review of the GWAS catalog for genes associated with multiple autoimmune diseases (Buniello et al., 2019; NHGRI, n.d.). Only genes associated with risk of at least three of the listed autoimmune diseases were included. *Study sample sizes:* 18% were <10,000 persons; 26% were 10,000–20,000 persons; 20% were 21,000–30,000 persons; 15% were 31,000–40,000 persons; 9% were 41,000–60,000; 9% were 86,000–116,000; and 3% was 755,400. *Study sample demographics:* The vast majority of study-sample populations were European. Some study samples included or were composed of Chinese, Asian, East Asian, Latin American, and Turkish populations.

AS, ankylosing spondylitis; ATD, autoimmune thyroid disease; IBD, inflammatory bowel disease (includes Crohn's disease and ulcerative colitis); MS, multiple sclerosis; PBC, primary biliary cholangitis / cirrhosis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; T1D, type 1 diabetes.

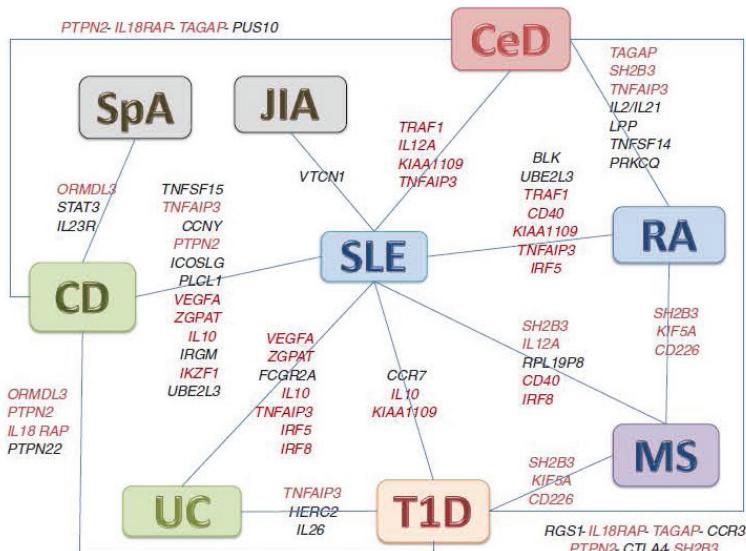
SOURCES: Acosta-Herrera et al., 2019; Anderson et al., 2011; Andlauer et al., 2016; Barrett et al., 2009; Barrett et al., 2008; Bentham et al., 2015; de Lange et al., 2017; Dubois et al., 2010; Ellinghaus et al., 2016; Eyre et al., 2012; Gulamhusein et al., 2015; Imgenberg-Kreuz et al., 2021; International Genetics of Ankylosing Spondylitis Consortium (IGAS) et al., 2013; International Multiple Sclerosis Genetics Consortium (IMSGC), 2019; International Multiple Sclerosis Genetics Consortium (IMSGC) et al., 2013; Jostins et al., 2012; Khatri et al., 2020; Kochi, 2016; Langefeld et al., 2017; Lessard et al., 2016; Li et al., 2015; Márquez et al., 2018; Morris et al., 2016; Okada et al., 2014; Onengut-Gumuscu et al., 2015; Qiu et al., 2017; Radstake et al., 2010; Saevarsdottir et al., 2020; Sawcer et al., 2011; Stahl et al., 2010; Todd et al., 2007; Tsoi et al., 2012, 2017; Wang et al., 2018, 2021; Wellcome Trust Case Control Consortium et al., 2007.

idiopathic arthritis, further highlighting commonalities among autoimmune diseases.

Determining genetic risk for autoimmune disease is complex because many different genes may be associated with the risk for the disease. Polygenic risk scores are used to convert the complexity of the multiple genetic risk variants into a single quantified measure (NHGRI, 2020). Studies defining polygenic risk scores for specific autoimmune diseases have demonstrated potential utility in diagnosis, prognosis, and molecular subsetting of autoimmune diseases. Recent studies in systemic lupus erythematosus (SLE) found associations of increased organ damage and mortality in individuals with high genetic risk scores (Reid et al., 2020). Another study focused on genes in different immunological pathways in order to identify different molecular subsets of individuals with SLE based on pathway-specific genetic risk scores (Sandling et al., 2021). Genetic risk scores have been used in studies of other autoimmune diseases such as type 1 diabetes (Sharp et al., 2018), multiple sclerosis (de Mol et al., 2020; van Pelt et al., 2013), and systemic sclerosis (Bossini-Castillo et al., 2021). In inflammatory bowel disease (IBD), genetic risk scoring is less well-established but shows some promise (Abakkouy and Cleynen, 2021). Advantages of genetic risk scores include the ease of a standardized measurement and the absence of disease activity-based variability that can complicate measures of other disease-associated biomarkers (Sharp et al., 2018). Disadvantages include risk scores that represent relative risk rather than absolute risk, and that their applicability to the general population will require studying more diverse populations. Much of the available genomics data are based on individuals of European ancestry, which makes the relevance of these risk scores less clear for other populations (NHGRI, 2020). Moreover, the overlap in genetic risk between autoimmune diseases such as systemic sclerosis and SLE, Sjögren's disease, or rheumatoid arthritis may preclude the ability to accurately distinguish the diseases based on genetic risk scores alone (Bossini-Castillo et al., 2021). Thus, additional studies are needed to overcome the limitations of polygenic risk scores before they can be used clinically, but such studies are warranted to help shift the diagnosis and treatment of autoimmune diseases to prediction and prevention.

Despite clear associations between genetic variants of immune-related genes and specific autoimmune diseases, a complete understanding of the specific effects of these variants in the pathogenesis of these diseases is lacking. The altered biological functions of the genetic variants and their roles in immune dysregulation remain gaps in our knowledge of the genotype–phenotype relationships of disease-associated genetic variants. An important focus of future research will be to systematically map the biologic function of genetic variants for the different autoimmune diseases. Defining the functions of variant-related immune pathways is

critical as this knowledge can inform clinical approaches to modulate the dysregulated or overactive immune pathways. The same pathway may or may not function the same way across diseases. For example, the pathogenic role of tumor necrosis factor (TNF) in rheumatoid arthritis, inflammatory bowel disease, and psoriasis led to targeting therapies to block TNF to treat these diseases (Jang et al., 2021), but TNF inhibitors have negative effects in the treatment of multiple sclerosis (Kemanetzoglou and Andreadou, 2017). In some individuals without multiple sclerosis, treatment with TNF inhibitors can cause multiple sclerosis-like demyelination (Kemanetzoglou and Andreadou, 2017). Despite effectively treating psoriasis in many individuals, the use of TNF inhibitors may also induce psoriasis (Mazloom et al., 2020). Similarly, genetic variants may have opposite effects in different autoimmune diseases and be associated with protective effects in some autoimmune diseases but with increased risk in others (Dendrou et al., 2016; Wang et al., 2010). Beyond associations of gene



**FIGURE 4-2** Overlap of associated loci among select autoimmune diseases, including seven of the diseases reviewed in Chapter 3. Loci depicted in red are those shared by more than two autoimmune diseases. Loci depicted in black are those shared by only two autoimmune diseases.

NOTES: There are more recent data, and the data continually grow. This figure is not intended to be comprehensive.

CD, Crohn's disease; CeD, celiac disease; JIA, juvenile idiopathic arthritis; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthropathy; T1D, type 1 diabetes; UC, ulcerative colitis.

SOURCE: Richard-Miceli and Criswell, 2012.

variants with autoimmune diseases, altered expression of genes through epigenetic modifications may drive differential effects of immune-related genes (Mazzone et al., 2019).

**Finding:** Studies of genetics in autoimmune diseases have identified genes associated with specific autoimmune diseases. The overlap in genes associated with different autoimmune diseases underscores the contribution of non-genetic factors, such as environmental exposures, in determining which organ systems are targeted by the autoimmune response, but the mechanisms of the genotype–phenotype associations are not known.

**Finding:** Studies have consolidated the complex gene variants into a single genetic risk score to define genetic risk for a specific autoimmune disease. However, the majority of available data driving genetic risk scores are based on individuals of European ancestry.

**Conclusion:** *Genetic risks are common and often overlapping in autoimmune diseases, but more research is needed to define these risks in different populations in order to develop more widely applicable genetic risk scores and to promote studies to define genotype-phenotype associations.*

### Environmental Factors

Studies of the incidence of autoimmune disease in identical and fraternal twins show that autoimmune diseases may require an environmental signal or exposure to develop (Figure 4-3). Nationwide or population-based twin registry or cohort studies comparing the incidence of SLE (Ulff-Møller et al., 2018), type 1 diabetes (Nistico et al., 2012), multiple sclerosis (Willer et al., 2003), and Graves' disease (Brix et al., 2001) find probandwise concordance rates of 25 to 45 percent in identical twins and much lower rates, ranging from 5 to 16 percent, in fraternal twins, implying strong genetic factors and the need for a “second hit”—presumably environmental exposure—for the development of autoimmune disease. Investigators found a lower concordance rate of 9.1 percent in identical twins in rheumatoid arthritis, similar to the 6.4 percent concordance rate seen in fraternal twins (Svendsen et al., 2013). In systemic sclerosis, identical and fraternal twins both had a 5 percent concordance rate (Feghali-Bostwick et al., 2003), suggesting more environmental and less genetic influence on disease development.

Because they depend on diagnosis definition and duration of observation, concordance rates may mislead. For example, in a restudy that applied new technology to examine twin concordance rates fifteen years

after an earlier study, the researchers showed that SLE markers had been present in the well twins of the earlier study (Reichlin et al., 1992), and thus the well twins had been serologically but not clinically concordant with their siblings. The restudy also showed that some well twins developed clinical illness, becoming clinically concordant, decades after their twin siblings were first diagnosed. These observations strongly support the “second-hit” hypothesis, which holds that a genetic profile requires an additional exposure event to become clinical illness. Examples of exposures associated with autoimmune diseases include infectious agents, pesticides, solvents, endocrine-disrupting chemicals, occupational exposure to respirable particulates and fibers, and personal factors such as cigarette-smoking history and diet preferences (Cooper et al., 2009; Cunningham, 2019; Diegel et al., 2018; Hahn et al., 2022; Khan and Wang, 2019; Parks et al., 1999; Popescu et al., 2021).

### *Infections*

For some autoimmune diseases, such as rheumatic fever, myocarditis, multiple sclerosis, rheumatoid arthritis, and SLE, research has identified a causal link between bacterial or viral infection and the development of disease (Bjornevik et al., 2022; Cunningham, 2019; Fairweather et al., 2001, 2003; Fechtner et al., 2021; Jog et al., 2019; Lanz et al., 2022; McClain et al., 2005). For example, data have found that infection with or reactivation of Epstein-Barr virus precedes development of multiple sclerosis, rheumatoid arthritis, and SLE (Bjornevik et al., 2022; Fechtner et al., 2021; Jog et al., 2019; Lanz et al., 2022; McClain et al., 2005).

Additionally, research has found associations between type 1 diabetes and coxsackievirus and cytomegalovirus infections (Fairweather et al., 2001; Rodriguez-Calvo, 2019); multiple sclerosis and Epstein-Barr virus (Bjornevik et al., 2022) and measles infections (Mentis et al., 2017; Persson et al., 2014; Tucker and Andrew Paskauskas, 2008); and rheumatoid arthritis and mycobacteria and Epstein-Barr virus infections (Fairweather et al., 2012). However, most of the associations between infectious agents and autoimmune diseases are considered to be circumstantial. Linking an infection to an autoimmune disease is problematic because there is usually an extended period between the infection and the appearance of clinical autoimmune disease. The best evidence that infectious agents can cause autoimmune disease comes from animal studies in which researchers administered self-antigens with adjuvant incorporating non-infectious microbial antigens (Fairweather et al., 2001). A variation on the classic experimental autoimmune model uses an injection of heart- or salivary gland-derived cytomegalovirus or coxsackievirus B3 as the trigger to

induce myocarditis, which is associated with the development of autoantibodies against cardiac myosin (Fairweather et al., 2001).

Some of the best clinical evidence that viral infections can cause an autoimmune disease comes from the ability of SARS-CoV-2 to cause myocarditis, which occurs in approximately 4.5 percent of COVID-19 cases (Kawakami et al., 2021). SARS-CoV-2 has also been associated with the production of multiple autoantibodies and the development of autoimmune diseases besides myocarditis such as antiphospholipid syndrome, Guillain-Barré syndrome, and Kawasaki disease (Dotan et al., 2021). The production of autoantibodies after viral infections is a feature of animal models of virally induced autoimmune disease (Fairweather et al., 2001), further indicating this as an important area for future investigation. Multiple diverse microorganisms have been associated with a single autoimmune disease—for example, several different viral infections are associated with myocarditis—which suggests that infectious agents induce autoimmune disease through common mechanisms (Fairweather and Rose, 2006). Similarly, infection by one microorganism may induce different autoimmune diseases. Coxsackievirus is associated with type 1 diabetes (Rodriguez-Calvo, 2019), autoimmune thyroiditis (Hashimoto's thyroiditis) (Mori and Yoshida, 2010), and myocarditis (Tam, 2006), and in children, SARS-CoV-2 infection is linked to myocarditis (Boehmer et al., 2021) and Kawasaki-like inflammatory disease (Dotan et al., 2021) as well as multisystem inflammatory syndrome (Consiglio et al., 2020). The inflammatory response to infection may play a greater role in causing autoimmunity than the specific infectious agent; the inflammation activates common pathogenic mechanisms that cause autoimmune disease. Inherent in this observation is that common innate immune factors such as Toll-like receptor 2 (TLR2) and/or TLR4 are able to initiate the autoimmune response to infectious agents (Mohammad Hosseini et al., 2015).

There are a number of theories for how infections or other environmental agents can trigger autoimmunity and autoimmune disease. These include (Cavalli and Heard, 2019; Fairweather and Rose, 2006; Surace and Hedrich, 2019):

- direct viral damage;
- release of cryptic self-peptides, which are antigens that are normally exposed to the immune system in such low amounts that the body has not developed self-tolerance<sup>1</sup> to them;

<sup>1</sup> Self-tolerance refers to the immune system's tolerance to the body's own antigens (self-antigens). By this mechanism, the immune system prevents the production of functional B cells and T cells that react to self-antigens and prevents the body from directing an immune response against itself. Impairment of this mechanism leads to autoimmunity and production of autoantibodies against self-antigens (Hale et al., 2005).

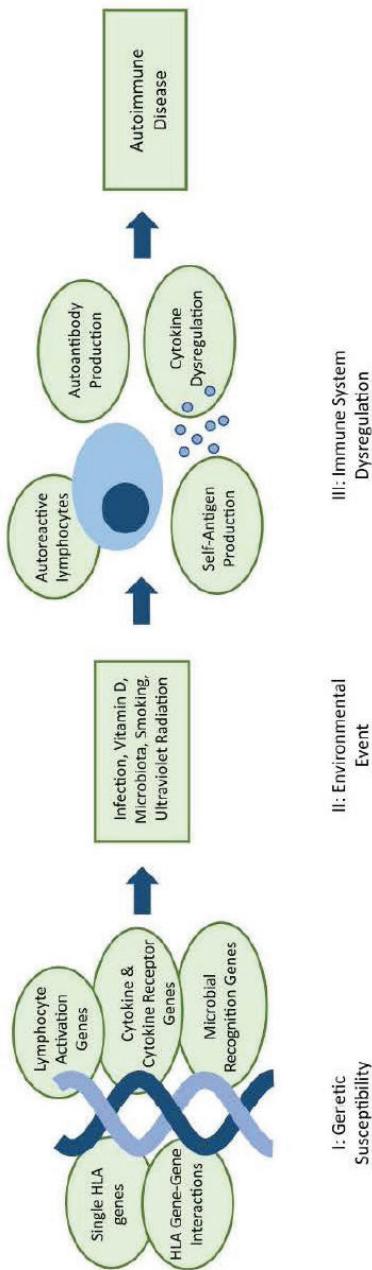
- antigenic spread, which occurs when the immune system's response to a microbial antigen expands to include similar self-antigens;
- molecular mimicry, which occurs when a microbial antigen closely resembles a self-antigen;
- epigenetics;
- bystander activation, which occurs when the immune system is activated in an antigen-independent manner and then produces a cytokine storm; and
- an adjuvant effect, which occurs when a microbial antigen or chemical adjuvant activates the innate immune response to self-tissue. Support for the latter comes from animal experiments in which researchers induce autoimmune disease using self-peptides and adjuvants; examples include inducing rheumatoid arthritis by administering collagen with an adjuvant, multiple sclerosis by inoculating with myelin basic protein with an adjuvant, and myocarditis by injecting cardiac myosin with an adjuvant.

Other hypotheses hold that co-infections with bacteria and viruses are necessary to induce autoimmune disease or that autoimmunity may occur commonly as a normal response needed to clear damaged self (Root-Bernstein and Fairweather, 2015).

#### *Respiratory Exposures: Silica, Asbestos, and Tobacco Smoke*

The research pertaining to respirable silica exposure and systemic autoimmune diseases—rheumatoid arthritis, SLE, systemic sclerosis, and various forms of small-vessel vasculitis—spans more than 100 years (Parks et al., 1999). A robust set of studies, with highly consistent findings from a variety of populations and settings and using different study designs, have demonstrated at least a 2- to 4-fold increased risk of developing each of those diseases associated with occupational exposure to silica (Figure 4-4). The figure's inclusion of data on 2 of the 11 diseases of focus as well as systemic sclerosis and vasculitis highlights the risk silica exposure carries across autoimmune diseases.

Studies have also investigated immune-related effects of silica in the lung. Silica stimulates macrophages and also leads to their destruction, releasing intracellular self-antigens and stimulating proinflammatory cytokines, including interleukin 1 (IL-1) and TNF, and eventually activating the innate and adaptive immune response in the lungs and other tissues (Bates et al., 2015; Brown et al., 2003; Chauhan et al., 2021; Cooper et al., 2008; Foster et al., 2019). Studies of a breed of mice susceptible to SLE have examined the mechanisms by which inhaled silica induces both

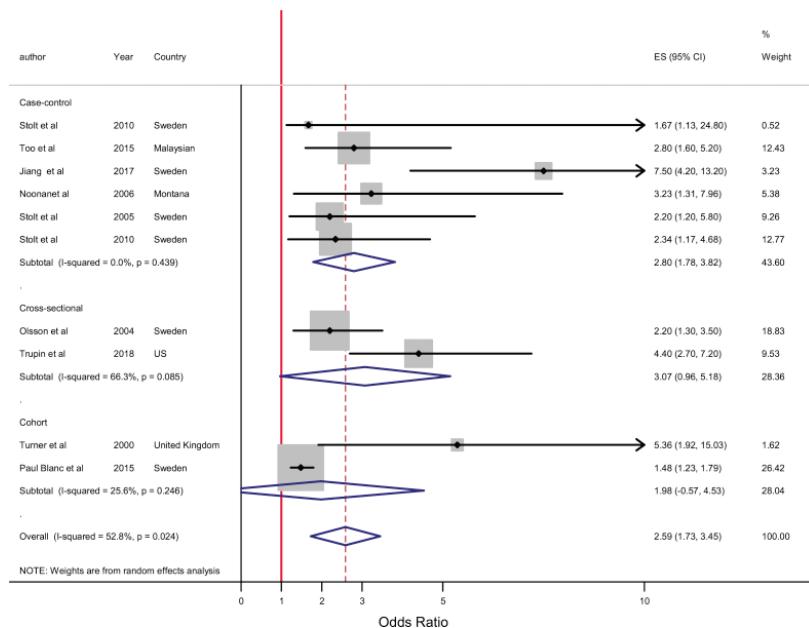


**FIGURE 4-3** Three factors contributing to autoimmune disease development. I. Genetic susceptibility is conferred by a combination of genes that may include genes encoding human leukocyte antigen innate and adaptive immune proteins, and directly or indirectly affect the regulation of the immune system. II. Examples of potential environmental triggers for dysregulation. III. Autoantibody production alone will not always result in disease development; self-antigen production and subsequent elevated immune response is necessary.

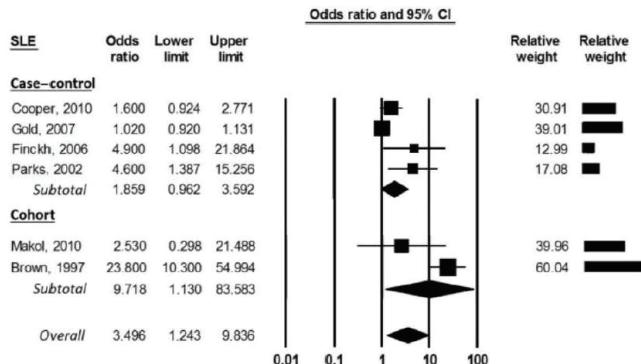
NOTE: HLA, human leukocyte antigen.

SOURCE: Reprinted with permission from Stafford et al., 2020.

### A. Rheumatoid Arthritis



### B. Systemic Lupus Erythematosus



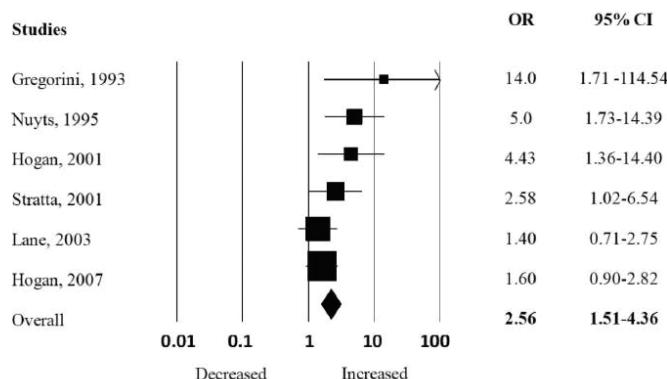
**FIGURE 4-4** Forest plots from meta-analyses of epidemiologic studies of the association between occupational silica exposure and systemic autoimmune diseases. A. Rheumatoid arthritis. B. Systemic lupus erythematosus. C. ANCA-associated vasculitis. D. Systemic sclerosis (scleroderma).

NOTES: More recent studies in each of these diseases provide additional support for this association (Boudigaard et al., 2021; De Decker et al., 2018; Giorgiutti et al., 2021; Ilar et al., 2019).

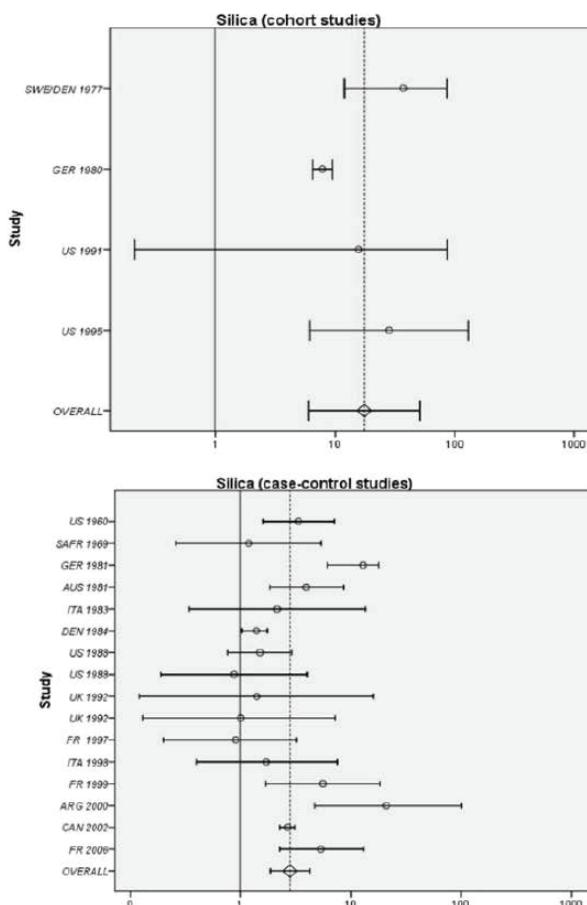
ANCA, antineutrophil cytoplasmic antibody; CI, confidence interval; ES, effect size; OR, odds ratio.

SOURCES: A. reproduced from Mehri et al., 2020. B. reproduced from Morotti et al., 2021. C. reproduced from Gómez-Puerta et al., 2013. D. reproduced from Rubio-Rivas et al., 2017.

## C. ANCA-Associated Vasculitis



## D. Systemic Sclerosis

**FIGURE 4-4** Continued

development and exacerbation of SLE and activates immune responses outside the lung (Bates et al., 2015; Brown et al., 2003; Chauhan et al., 2021; Foster et al., 2019). Examining silica in combination with other exposures has also been revealing. A recent study using a breed of mice that is not prone to autoimmune disease found that an early-life exposure to lymphocytic choriomeningitis virus followed later by a single high-intensity airway exposure to silica in the adult mice produced lupus-related autoantibodies and kidney lesions (Gonzalez-Quintial et al., 2019).

Recent research has expanded the interest in respirable exposures to other particles and fibers. Several studies have examined systemic autoimmune diseases and autoantibodies in populations exposed to various forms of asbestos and asbestiform particles in Montana and in Australia, Italy, Korea, and Sweden (Carey et al., 2021; Diegel et al., 2018; Ilar et al., 2019; Lee et al., 2020; Noonan et al., 2006; Pfau et al., 2018; Rapisarda et al., 2018; Reid et al., 2018), and experimental studies have examined the effects of asbestos on macrophages, T cells, and cytokine profiles (Ferro et al., 2014; Khaliullin et al., 2020; Kumagai-Takei et al., 2020). An emerging area of research is exploring the effects on inflammation and autoimmune disease of a severe and sudden high-intensity mixture of respirable exposures, or the combination of these exposures with highly stressful conditions, such as experienced during the September 11, 2001, World Trade Center attacks and during natural disasters such as earthquakes and tsunamis. With respect to the respirable occupational exposures noted above, the question of relevant exposure level—the combination of intensity and duration needed to induce autoimmune disease—and whether current occupational exposure limits are sufficient to prevent adverse autoimmune disease, is a crucial question that further research needs to address.

Cigarette smoking is a well-studied risk factor for many forms of cancer, cardiovascular disease, and other conditions, and for some autoimmune diseases there are relatively strong data supporting an association, including evidence of a dose-response relationship between the intensity and duration of cigarette smoking and the likelihood of developing an autoimmune disease. This is seen, for example, with rheumatoid arthritis, particularly in people with rheumatoid factor or anti-citrullinated protein peptide antibodies (Costenbader and Karlson, 2006; Liu et al., 2019), and Graves' disease, particularly in people with Graves' ophthalmopathy (Vestergaard, 2002). Studies have identified weaker associations between current smoking and SLE and multiple sclerosis (Belbasis et al., 2015; Parisis et al., 2019). Somewhat paradoxically, smoking is associated with an increased risk and severity of Crohn's disease, but with a reduced risk of developing ulcerative colitis (Piovani et al., 2021); smoking cessation has been shown to increase the risk of developing ulcerative colitis in the Western world (Ananthakrishnan et al., 2020). Studies in Western cohorts,

however, have consistently demonstrated that smoking increases the risk and severity of Crohn's disease (Ananthakrishnan et al., 2020). Research has also found that smoking is associated with severity, progression, risk of flares, or treatment effectiveness in several other autoimmune diseases (Costenbader and Karlson, 2006; Hedström et al., 2021; Parisis et al., 2019; Simmons et al., 2021).

### *Other Occupational and Environmental Exposures*

Studies have examined the relationship of exposure to the broad category of solvents and the development of several autoimmune diseases. In 2010, an expert panel concluded that evidence from epidemiologic studies provided "confidence that solvent exposure contributes to the development of systemic sclerosis (scleroderma)," while the panel considered a link between solvent exposure and multiple sclerosis to be "likely but requiring confirmation" (Miller et al., 2012; Parks et al., 2014). Regarding specific solvents, studies of trichloroethylene exposure in animal models found disease acceleration in lupus-prone mice, markers of inflammatory response, and the development of autoimmune hepatitis, inflammatory skin lesions, and alopecia. Human studies have produced similar findings in workers exposed to trichloroethylene (Cooper et al., 2009). There is a need for further research focusing on the effects of specific solvents in experimental and epidemiologic studies.

Endocrine-disrupting chemicals—bisphenol A (BPA), a variety of phthalates, polybrominated flame retardants, perchlorate, perfluorinated chemicals, polychlorinated biphenyls, dioxins, and some types of pesticides and herbicides, among others—are another broad category of compounds of particular relevance to the general population because of the potential for exposure through environmental contamination as well as through food, food packaging, and personal care and home products (Diamanti-Kandarakis et al., 2009). Exposure to endocrine-disrupting chemicals *in utero* also carries the potential to affect DNA methylation and genomic imprinting; this early-life exposure can carry risk for disease even in adulthood (Robles-Matos et al., 2021). Biomonitoring data from the National Health and Nutrition Examination Survey have revealed a high prevalence and widely varying levels of exposure to many of these compounds in the U.S. population (EPA, 2021). Endocrine-disrupting chemicals such as phenols (e.g., BPA), parabens, and phthalates have been shown to influence sex hormone activity and alter immune responses in animals and may influence sex differences in autoimmune diseases as has been found for viral myocarditis in mice (Bruno et al., 2019; Castro-Correia et al., 2018; Edwards et al., 2018; Popescu et al., 2021). Compounds within this category may exhibit estrogenic, antiandrogenic, or thyroid

hormone effects, including disruption to hormone binding, synthesis, secretion, transport and metabolism. There is a growing body of research pertaining to effects of specific compounds or classes of chemical compounds on immune function (Nowak et al., 2019), but there has been relatively little focused research to date within the context of autoimmunity or autoimmune diseases.

### *Dietary Exposures*

As Chapter 3 described, autoimmune diseases share several diet-related risk factors (Table 4-1), suggesting common etiologies and mechanisms. Several of the shared dietary risk factors, including breast milk, gluten, vitamin D, omega-3 fatty acids, and sugars, play a significant role in shaping the gut microbiome (Hamilton-Williams et al., 2021), and researchers theorize that these dietary components may interact with the microbiome to stimulate a mucosal immune response. Alternatively, or in addition, dietary intake influences the inflammatory state of the body, which may also play a role in the development of autoimmune diseases. Although vitamin D is considered a vitamin, it is actually a steroid hormone that binds to the vitamin D receptor with downstream transcriptional regulation of many genes (Tintut and Demer, 2021), and similar to other steroid hormones, vitamin D strongly influences immune responses (Park and Han, 2021).

Research has also found that proinflammatory dietary factors, such as red meat and sugar-sweetened beverages, are associated with increased risk of rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes, whereas anti-inflammatory dietary factors, such as omega-3 fatty acids, have been associated with decreased risk of type 1 diabetes and rheumatoid arthritis. The recently published Vitamin D and Omega 3 Trial found that supplementation with vitamin D led to a 22 percent reduction in all incident autoimmune diseases, and supplementation with marine omega-3 fatty acids (fish oil) with or without vitamin D led to a (nonsignificant) 15 percent reduction in all incident autoimmune diseases during 5 years of randomized follow-up of more than 25,800 older adults from the general population (Hahn et al., 2022). The study was not adequately powered to examine the effect of supplementation on individual autoimmune diseases. The list of shared dietary risk factors in Table 4-1 was limited to those observed in prospective studies. It is likely that additional prospective investigations of diet in other autoimmune diseases would uncover more shared dietary risk factors, thereby providing clues into shared etiologies and mechanisms. Additionally, systematic collection of longitudinal data on dietary exposures would enable examination of their role in development, progression, and mitigation of autoimmune diseases.

**TABLE 4-1** Shared Dietary Risk Associations Across Autoimmune Diseases

Dietary Factor	Increased risk for:						
	T1D	Celiac Disease	UC	Crohn's Disease	RA	SLE	
No breast feeding in infancy							
Lower vitamin D intake/25OHD level							
Lower omega-3 fatty acid intake/status							
Higher gluten intake in early childhood							
Higher sugar/sugar-sweetened beverage intake							
Higher meat/animal protein intake							

NOTES: Dietary factors listed in the left column are associated with autoimmune diseases listed across the top as indicated by a filled black box.

MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; UC, ulcerative colitis; 25OHD, 25-hydroxyvitamin D.

SOURCES: No breast feeding: T1D (Lund-Blix et al., 2017), UC and Crohn's disease (Barclay et al., 2009; Klement et al., 2004; Ng et al., 2015). Lower omega-3 fatty acids: T1D (Norris et al., 2020), RA (Di Giuseppe et al., 2014; Gan et al., 2016, 2017a,b). Lower Vitamin D/25OHD: T1D (Miettinen et al., 2020), Crohn's disease (Ananthakrishnan et al., 2012), SLE (Hassanalilou et al., 2018; Young et al., 2017), MS (Munger et al., 2006). Higher gluten: celiac disease (Andrén Aronsson et al., 2019), T1D (Norris et al., 2020). Sugar/sugar-sweetened beverage intake: T1D (Norris et al., 2020), UC (Racine et al., 2016), RA (Hu et al., 2014). Higher meat/animal protein: Crohn's disease and UC (Hou et al., 2011; Jantchou et al., 2010), RA (Pattison et al., 2004).

The preceding discussion of environmental factors provides a foundation for considering potential approaches to preventing the occurrence of autoimmune diseases. Some approaches are based outside of the health care system such as advertising efforts to discourage smoking or worksite interventions to reduce levels of respirable silica exposure. Other approaches rely on health care provider interactions with individuals, including efforts to identify people at high(er) risk for developing autoimmune diseases; monitor biomarkers of disease development such as type 1 diabetes-linked antibodies; apply exposure interventions; and use pharmaceutical agents that research shows can reduce disease risk, as seen in ongoing studies for type 1 diabetes and rheumatoid arthritis.

**Finding:** Environmental factors such as infection, occupational exposure to respirable silica, solvents, and diet have been implicated in multiple autoimmune diseases, and the same individual environmental factor may also be associated with multiple autoimmune diseases. Evidence suggests that genetic predisposition may work in concert with environmental exposures to cause autoimmune disease; moreover, there is evidence to suggest that both genetic and environmental exposure must be present in order for disease to develop. The role of environmental exposures in disease progression and flares is an important area requiring additional research.

*Conclusion: Research is needed to define the type and duration of environmental exposures associated with development and progression of autoimmune diseases, including disease flares, both for specific diseases and across diseases. Similarly, further research is needed to identify the permutation of genes and environmental exposures that lead to autoimmune diseases. In addition, investigations into how dietary antigens and other environmental exposures interact with the microbiome are needed.*

### **Inflammation, Autoantibodies, and Mechanisms of Autoimmune Disease**

The presence of autoantibodies is a common feature of autoimmune diseases, as is the presence of inflammatory cells such as mononuclear phagocytes, autoreactive T lymphocytes and autoantibody-producing B cells. Autoantibodies play a key role in disease diagnosis, and they may be pathogenic in some cases when they bind to self-tissues, activate the complement cascade, and instigate cell destruction and/or clearing cell debris (Burbelo et al., 2021; Daha et al., 2011). They can also interact with and alter the function of cell-surface receptors, as is the case in myasthenia

gravis and Graves' disease (Chain et al., 2020; George et al., 2021; Kojima et al., 2021).

Immune system cells induced during inflammation can play a major pathogenic role in many autoimmune diseases, either by killing cells directly or by releasing cytotoxic cytokines, prostaglandins, or reactive nitrogen or oxygen intermediates. At the same time, other immune system cells, such as suppressor or regulatory T cells, function as a counterbalance in controlling inflammation and autoimmune responses by killing self-reactive T cells and releasing anti-inflammatory cytokines. Disrupting the regulation of self-reactive T cells and autoantibody production by regulatory T cells may result in the development of autoimmunity. Similarly, breaking tolerance against self-antigens may trigger the development of autoimmune disease (Abbas et al., 2004; Marx et al., 2021; Nelson, 2004). Self-tolerance develops through carefully regulated mechanisms, and defects in one or more of these mechanisms may lead to autoimmune disease development.

Inoculating animals with self-antigen in combination with adjuvants that activate the immune response enables investigators to produce animal models that recreate many of the features of human autoimmune diseases (see Chapter 3 for more information on animal models for specific autoimmune diseases). Injecting adjuvants without self-antigen or self-antigen without adjuvants does not usually result in the development of autoimmune disease. Thus, in the context of presentation of self-antigen that occurs presumably as a result of viral infection or chemical exposure, it is necessary to activate the innate immune system in order to develop the adaptive immune response (i.e., a T cell and B cell response) that progresses to autoimmune disease. Adjuvant-stimulated collagen-induced rheumatoid arthritis and cardiac myosin-induced myocarditis are examples of this type of animal model (Fontes et al., 2017). The self-antigens that are responsible for causing autoimmune disease have been identified for a number of autoimmune diseases including cardiac myosin for myocarditis (Myers et al., 2013), myelin basic protein or myelin oligodendrocyte glycoprotein for multiple sclerosis (Martinsen and Kursula, 2022; Yannakakis et al., 2016), and collagen for rheumatoid arthritis (Allen et al., 2019; Liang et al., 2019). However, the autoantigens associated with most autoimmune diseases remain unknown. Identifying new autoantigens is necessary in order to develop new animal models of disease, to better detect autoantibodies and autoreactive T cells, and to develop new and more effective therapies.

Increased production of the proinflammatory cytokines TNF and IL-1 $\beta$  are also involved in the development of some autoimmune diseases. Injecting strains of mice that are genetically susceptible to developing autoimmunity with either of these cytokines, or with certain adjuvants

(i.e., lipopolysaccharide that binds to TLR4 releasing IL-1 $\beta$ ) that stimulate their production, can accelerate autoimmune disease. Repeating the same experiment with genetically resistant mouse strains can break self-tolerance and lead to autoimmunity (Lane et al., 1992, 1993). This suggests that environmental factors can overcome genetic resistance to developing autoimmune disease.

### Disease Predictors

A number of biomarkers obtained from serum, tissues, or other sources have been used to predict the development of an autoimmune disease, to confirm diagnosis, or to predict the outcome of disease, such as autoantibodies, cytokines, microRNAs, and T cell–B cell interactions.

Autoantibodies are common in autoimmune diseases, and, while their role in the disease pathogenesis is not always clear, detecting them in clinical specimens may aid in diagnosing or, in some cases, predicting disease. In type 1 diabetes, perhaps the most studied autoimmune disease, autoantibodies that target intracellular autoantigens prior to the patient developing autoimmune pathology are detectable many years prior to the onset of clinical symptoms (Burbelo et al., 2021; Leslie et al., 2001). The risk of developing type 1 diabetes within 5 years increases from approximately 10 percent when a blood sample shows one autoantibody to 60 to 80 percent when it shows three autoantibodies (Notkins, 2004; Ziegler et al., 2013). In SLE, autoantibodies can be detected in blood samples taken years before the clinical features of the disease appear (Arbuckle et al., 2003), and researchers have proposed that detecting autoantibodies or other measures of inflammation may be predictors of disease (Lambers et al., 2021). Similarly, studies have detected autoantibodies up to 20 years before diagnosis of Sjögren’s disease (Theander et al., 2015), and years in advance of clinical manifestations or diagnosis of other autoimmune diseases, including rheumatoid arthritis, systemic sclerosis, celiac disease, thyroid disease, and others (Burbelo et al., 2021; Leslie et al., 2001).

The ability to reliably predict the development of autoimmune diseases is an opportunity to intervene to prevent or delay development of clinical manifestations of disease and to improve outcomes. New, exciting data are now available for many autoimmune diseases, some more advanced than others, and additional studies are needed to better define the complex components driving risk to developing disease.

In type 1 diabetes, research has included focusing on genetic risk factors, exposures in infancy or before birth, and development of autoantibodies in the first years of life (Anand et al., 2021; Bonifacio et al., 2021; Frederiksen et al., 2013; Jacobsen et al., 2015; Krischer et al., 2019; Ng et

al., 2022; Ziegler et al., 2013). Such studies have made predicting disease development reliable enough to justify preventive intervention in those at high risk. The Global Platform for the Prevention of Autoimmune Diabetes Primary Oral Insulin Trial is randomizing infants with a > 10 percent risk for developing multiple autoantibodies, which in turn predicts high risk for type 1 diabetes, to receive daily oral insulin or placebo. To determine whether the intervention prevents development of autoantibodies or progression to diabetes, investigators will follow the infants up to 7 years (Ziegler et al., 2019). Because the trial participants have not yet developed evidence of autoimmunity but are at risk for doing so, it is a primary prevention trial (Primavera et al., 2020). In a secondary prevention trial, nondiabetic relatives of individuals with type 1 diabetes who were at high risk for development of disease (defined as having two or more autoantibodies and dysglycemia but not overt diabetes) were randomized to a T cell-targeting therapy or placebo and monitored for the progression to clinical diagnosis of diabetes (Herold et al., 2019). Treatment delayed progression to diagnosis of diabetes. Given that treatment is not risk free, justification for its use requires highly reliable prediction of high-risk individuals.

Similar studies, although less advanced, are in progress to define predictive measures and preemptive interventions for rheumatoid arthritis (Deane and Holers, 2021). Genetic risk scores and certain autoantibodies inform the predictive power; documented dietary and infectious exposures can enhance prediction and provide targets for intervention (Primavera et al., 2020). In addition, recent data in the study of SLE indicate that antibody to Ro52 may predict which pre-diagnosis patients will progress to diagnosable disease (Muñoz-Grajales et al., 2021).

Cytokine profiles can also be used as biomarkers. For example, the type I, II, and III interferon (IFN) cytokines are involved in SLE (Idborg and Oke, 2021), and most patients with SLE have an augmented expression of IFN-regulated genes, termed an “IFN gene signature,” with type I IFNs contributing most to the signature (Capecchi et al., 2020; Ramaswamy et al., 2021). Circulating levels of IFN- $\alpha$  correlate with disease activity and potentially could be used as a disease biomarker (Idborg and Oke, 2021). However, levels of IFN- $\gamma$  have been shown to rise years before both type I IFN activation and clinical presentation of SLE. In addition, the patterns of cytokine increases vary with different clinical manifestations of SLE. Further research in this area will likely yield novel biomarkers.

Another potential biomarker is to use a combination of cytokines (soluble ST2, IL-6), immune cell responses (Th17), and micro RNAs to diagnose and/or predict worse outcome in myocarditis. Soluble ST2 is a cytokine in the TLR4/IL-1R family that has been found to be elevated in men and male mice with myocarditis and to be associated with worse

outcome (Coronado et al., 2019). The cytokines IL-1 $\beta$  and IL-6, necessary for the development of Th17-type immune responses, have been found to be elevated in men with myocarditis where Th17 responses were found to be associated with poor outcome, but only in men (Myers et al., 2016). In addition, a microRNA associated with Th17 cells was identified in viral and autoimmune animal models of myocarditis that enabled researchers to distinguish myocarditis from other forms of inflammatory heart disease (Blanco-Domínguez et al., 2021). These immune pathways (TLR4/IL-1 $\beta$ /IL-6/Th17) are common to many autoimmune diseases and indicate the importance of identifying common pathogenic mechanisms that may reveal new biomarkers and therapeutic strategies to prevent disease.

Many autoimmune diseases involve pathologic T cell–B cell interactions, and more specifically, implicate PD-1<sup>hi</sup> CXCR5-T peripheral helper cells, which suggests that these T helper cells might be used as biomarkers of disease progression and as a target for therapy (Marks and Rao, 2022). Biomarkers also may be used to predict disease-activity changes such as flares of disease, as was recently reported using cytokines to identify renal and non-renal disease flares in individuals with SLE (Ruchakorn et al., 2019).

The most effective disease predictors will likely need to be combinations of biomarkers and/or algorithms rather than an individual biomarker.

**Finding:** Autoantibodies and other biomarkers are associated with autoimmune diseases, and the presence of autoantibodies has been detected before, and sometimes long before, clinical disease develops. An increase in proinflammatory cells, cytokines, and signaling pathways has been implicated in the development of autoimmune disease.

**Conclusion:** *Continued research is needed to identify traditional and novel biomarkers, such as autoantibodies, cytokines, and genetic risk factors, of autoimmune disease in order to predict, intervene to delay or modify outcomes, and possibly even prevent development of clinical illness.*

### Sex Differences

Most autoimmune diseases display a sex difference in incidence and severity of disease (Cooper and Stroehla, 2003). These differences may result from the differential effects of sex hormones; microchimerism, which is the presence of two genetically distinct cell populations in the same individual; specific genes on the X or Y chromosomes; X chromosome inactivation; and sex differences in the body's response to environmental factors. Of these, researchers consider sex hormones to be a

major contributor to the sex differences in autoimmune diseases because of their essential role in the normal physiologic function of cells, tissues, and organs and their well-defined and extensive role in regulating the immune system in normal and pathological conditions. Sex steroid hormone receptors are expressed in or on the surface of immune cells (Buskiewicz et al., 2016), and those expressed on the surface in particular influence the immune response, as they likely contribute to immune signaling by innate and adaptive immune receptors in a sex-specific manner (Benten et al., 1999a,b; Schlegel et al., 1999).

Estrogen activates B cells, resulting in increased antibody and autoantibody responses to infection, vaccines, and autoantigens (Fischinger et al., 2019). In contrast, androgens such as testosterone and dehydroepiandrosterone decrease B cell maturation, reduce B cell synthesis of antibody, and suppress autoantibody production in humans with SLE, for example (Cook, 2008; Flanagan et al., 2017; Gubbels Bupp and Jorgensen, 2018; Regitz-Zagrosek et al., 2008). Estrogen's ability to increase autoantibodies and T and B cell responses, which are adaptive immune system activities, could play a key role in the increased incidence and severity of many autoimmune diseases that occur more often in women than men, such as autoimmune thyroiditis, Sjögren's disease, SLE, and systemic sclerosis (Cooper and Stroehla, 2003; Fairweather et al., 2012), while androgen's ability to increase Toll-like receptors, mast cells, and macrophages, which are innate immune system activities, may drive autoimmune diseases in men (Fairweather et al., 2008; Gubbels Bupp and Jorgensen, 2018). However, while there is evidence that estrogen influences immune signaling pathways pivotal in autoimmune disease and that it affects antibody and autoantibody levels in autoimmune disease in different animal and tissue culture models with normal and diseased cells, the fact that estrogen levels rise substantially during pregnancy and that autoimmune disease activity does not increase during pregnancy, and in some diseases such as rheumatoid arthritis, decreases during pregnancy, suggests that more research is needed to understand the role of estrogen in autoimmune disease (Moulton, 2018). Additionally, other hormones that alter the immune response besides estrogen are released during pregnancy such as progesterone (Desai and Brinton, 2019; Piccinni et al., 2021; Ziegler et al., 2018), making it more complicated to understand the role of a specific hormones in the progression of autoimmune disease.

Environmental exposures can affect sex hormone activity. For example, endocrine disruptors such as BPA have been shown to alter sex hormone expression and ratio on/in immune and other cell types in a sex-specific manner (Böckers et al., 2020; Bruno et al., 2019), and there have been few studies on the role of endocrine-disrupting chemicals in autoimmune diseases (Bruno et al., 2019).

Sex hormones are not the only factors driving sex differences in autoimmune diseases. Other factors besides estrogen that could increase autoimmune disease in women include genes expressed on X chromosomes, as appears to be the case in SLE, for example (Umiker et al., 2014), and differential responses to stress, especially early in childhood (Dube et al., 2009). The global effect of sex hormones on immune cell phenotype and function that promotes systemic or organ-specific autoimmunity is a common mechanism that occurs among different autoimmune diseases in adults. The role of onset of autoimmunity prior to puberty also requires study.

**Finding:** Sex chromosomes, sex hormones, and the effects of environmental exposures on sex hormones appear to play a role in differences between males and females in the occurrence and pathogenesis of autoimmune disease.

**Conclusion:** Additional research is needed to illuminate the role of sex chromosomes, sex hormones, and the effect of environmental exposures on sex hormones in the development of autoimmune disease as this could inform diagnosis and treatment of autoimmune diseases.

### **Complications, Comorbidities, and Co-occurring or Overlapping Autoimmune Diseases**

People with autoimmune diseases commonly have complications, which are “sequelae or predictable consequences of a particular diagnosis” (Iezzoni, 2013); complications are considered a direct result of the autoimmune disease or its treatment and increase the risk of developing another health problem. Examples of complications that adversely affect prognosis and treatment are cardiovascular disease in patients with diabetes and colon cancer in patients with ulcerative colitis. Patients with autoimmune diseases may also suffer comorbidities, which “are diseases with unrelated etiology” (Iezzoni, 2013) that do not share causes, symptoms, or laboratory abnormalities with the autoimmune disease. A patient may also develop a co-occurring autoimmune disease, which is one that does not share symptoms or laboratory test results with the coexisting autoimmune disease. And finally, patients with autoimmune disease may suffer from an overlapping autoimmune disease, defined as the simultaneous presence of clinical and laboratory features of multiple autoimmune diseases—for example, SLE and rheumatoid arthritis, commonly known as “rhupus” (Antonini et al., 2020).

### *Complications of Autoimmune Diseases*

Complications of autoimmune diseases (Table 4-2) can be serious. Depression and anxiety are examples of complications that occur across a majority of autoimmune disorders. The occurrence of depression and / or anxiety in the broad range of autoimmune conditions may result from the psychological effects or from the social determinants of living with an autoimmune disorder (Martz et al., 2021), but research has not ruled out the possibility that the direct central nervous system effects of rheumatoid arthritis, SLE, and multiple sclerosis may play a role in inducing depression (Bai et al., 2016; Vallerand et al., 2018, 2019). Cardiovascular disorders, stroke, lymphoma, and renal failure complicate a number of autoimmune disorders. Sometimes complications are specific to the organ targeted by the autoimmune disorder. Hepatocellular carcinoma and portal hypertension, for example, result from cirrhosis, which occurs as a consequence of primary biliary cholangitis. It is critical for clinicians to be aware of the complications of the diagnosed autoimmune disease, to undertake appropriate screening for them, and to engage patients in self-management so that patients are knowledgeable about potential complications and successful preventive strategies, and thus will bring their symptoms to medical attention (Bodenheimer et al., 2002).

### *Co-occurring and Overlapping Autoimmune Disease*

Table 4-3 shows the likelihood of increased risk for co-occurrence of a second autoimmune illness for the autoimmune diseases examined in Chapter 3. There is one exception: risk is decreased for co-occurring multiple sclerosis and rheumatoid arthritis (Somers et al., 2009). Study of the patterns of co-occurrence may inform knowledge of pathophysiology and mechanistic pathways for all autoimmune illnesses. For instance, both genetic susceptibility and environmental agents, including diet, likely play a role in the pathogenesis of autoimmune diseases, but how they affect clinical phenotype is unknown. As with complications, it is critical for clinicians and patients to be aware of the symptoms of a second autoimmune disease when the patient has a diagnosed autoimmune disease that has a higher association with one or more other autoimmune diseases.

**Finding:** Co-occurring and overlapping autoimmune diseases are common; patients in these subsets differ from those with a single autoimmune disease.

**TABLE 4-2** Complications and Comorbidities Exhibited by More Than One Autoimmune Disease

	Depression and/or Anxiety	Cardio-vascular Disease	Stroke	Maternal/Fetal Complications	Peripheral Neuropathy and/or Other Neurologic Complications	Cancer <sup>a</sup>	Renal Complications	Eye Damage or Disease	Susceptibility to Infection <sup>b</sup>
Sjögren's Disease	X	X		X	X	X	X	X	X
Systemic Lupus Erythematosus	X	X	X	X	X	X	X	X	X
Antiphospholipid Syndrome	X	X	X	X	X		X	X	X
Rheumatoid Arthritis	X	X	X		X	X		X	X
Psoriasis	X	X	X						X
Inflammatory Bowel Disease	X			X		X	X	X	X
Celiac Disease	X				X	X			X
Primary Biliary Cholangitis	X					X <sup>c</sup>			X <sup>c</sup>
Multiple Sclerosis	X				X				X

Type 1 Diabetes	X	X	X	X	X		X	X	X
Autoimmune Thyroid Disease	X	X		X		X		X	X

<sup>a</sup>Susceptibility to cancer may be the result of autoimmune disease or autoimmune disease treatment.

<sup>b</sup>Susceptibility to infection may be the result of autoimmune disease or autoimmune disease treatment.

<sup>c</sup>In individuals with primary biliary cholangitis who have cirrhosis.

SOURCE: Chapter 3.

**TABLE 4-3** Autoimmune Diseases That Commonly Co-occur

	Co-occurring Autoimmune Disease										
	Sjögren's Disease	SLE	APS	RA	Psoriasis	IBD	Celiac Disease	PBC	MS	T1D	AITD
Index Autoimmune Disease											
Sjögren's disease		X		X				X			X
SLE	X		X	X							X
APS		X									
RA	X	X				X			*	X	X
Psoriasis						X					
IBD							X	X			
Celiac Disease		X				X		X		X	X
PBC	X										
MS					X	X				X	
T1D							X				X
AITD	X	X					X		X		

\*Inverse association between rheumatoid arthritis and multiple sclerosis (Somers et al., 2009).

NOTES: Choose an index disease in the far-left column and read horizontally across the row to identify co-occurring diseases.

AITD, autoimmune thyroid diseases; APS, antiphospholipid syndrome; IBD, inflammatory bowel disease; MS, multiple sclerosis; PBC, primary biliary cholangitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes.

SOURCE: Chapter 3.

**Conclusion:** Greater focus on patients with co-occurring and overlapping autoimmune diseases may provide insight into the pathophysiology and mechanistic pathways of autoimmune disease, better characterize this type of illness, and lead to better patient care.

### Common Mechanistic Pathways as Therapeutic Targets

Despite the considerable variation in clinical symptoms or targeted organs among the different autoimmune diseases, the specific mechanisms of immune-mediated damage that leads to the different clinical pictures may share common immune pathways. As discussed above, cytokines are key mediators of immune cell effector functions, either in stimulating other immune cells to propagate disease or in directly affecting target organ cells to cause damage. The identification of specific proinflammatory signaling pathways and their cytokines as pathogenic in autoimmune diseases has resulted in targeted therapeutics that aim to block their effects. Identifying TNF as an inflammatory cytokine in synovial fluid from individuals with rheumatoid arthritis and then demonstrating that blocking TNF ameliorated disease in a mouse model of inflammatory arthritis led to the study of TNF inhibitors in the treatment of rheumatoid arthritis (Feldmann and Maini, 2010). The Food and Drug Administration (FDA) has approved TNF inhibitors for treating a number of different autoimmune diseases in adults and children including rheumatoid arthritis, juvenile idiopathic arthritis, plaque psoriasis and psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), and uveitis (FDA, 2021). While TNF inhibitors have had a significant effect on the management of these autoimmune diseases for many individuals, they are not effective for everyone. Studies of those individuals who fail to respond adequately to currently available medications may help to elucidate additional cytokines or other immune pathways that can be targeted therapeutically.

As noted above, IL-1 is another cytokine that plays a pathogenic role in the inflammation associated with some autoimmune diseases. Clinical studies have shown that IL-1 inhibitors are effective and often life-saving in dampening the hyperinflammatory response in autoinflammatory diseases such as systemic juvenile idiopathic arthritis, monogenic autoinflammatory diseases such as cryopyrin-associated periodic syndromes, and cytokine storm syndromes including the hyperinflammatory response that may occur in children following SARS-CoV-2 infection (Jesus and Goldbach-Mansky, 2014; Malcova et al., 2021; Mehta et al., 2020; Tanner and Wahezi, 2020).

Type I interferons, a family of molecules that includes 17 different cytokines, have relevant roles in autoimmune diseases, as well as a key

role in anti-viral immune responses (Lazear et al., 2019). This latter role, along with the association of type I interferons with autoimmune diseases, may support the idea that viral infections participate in triggering autoimmunity. However, research has also suggested that dysregulation of the type I interferon system or stimulation of type I interferon production by endogenous triggers may be involved in the etiology of autoimmunity. One extreme example of the latter is the class of autoinflammatory diseases grouped as interferonopathies, which result from monogenic inborn errors of immunity that lead to upregulation of a type I interferon response (Sogkas et al., 2021).

Research has implicated type I interferons as playing a role in several non-monogenic autoimmune diseases based on measurements of interferons directly or, more commonly, with the detection of the interferon signature—a collection of genes that are upregulated in response to interferons. SLE is the prototypical type I interferon-associated autoimmune disease, but studies have also associated type I interferons with diseases such as Sjögren's disease, idiopathic inflammatory myopathies, and systemic sclerosis (Jiang et al., 2020). Many of the disease risk-associated gene variants shared among autoimmune diseases are also associated with type I interferon-mediated signaling pathways (Figure 4-1). Additional support for a pathogenic role for type I interferons came from the development of autoimmune manifestations following treatment with type I interferons for cancer or viral hepatitis infections. These manifestations included effects on immune-mediated thrombocytopenia, vasculitis, autoimmune thyroid disease, autoimmune hepatitis, Raynaud phenomenon, rheumatoid arthritis, myositis, psoriasis, interstitial nephritis, autoimmune colitis, and SLE, and product inserts for type I interferon drugs noted them as potential adverse effects of treatment (FDA, 2021). Other autoimmune diseases, such as multiple sclerosis, may actually improve with type I interferon treatment, suggesting that the role of type I interferons in driving autoimmunity is not absolute (FDA, 2021).

The pathogenic role of type I interferons in multiple autoimmune diseases or monogenic autoinflammatory diseases has led to developing treatments to target the type I interferon pathway; these include blocking type I interferons or the type I interferon receptor directly, or through small molecule inhibitors such as the Janus kinase (JAK) inhibitors that target key signaling components of the type I interferon signaling pathway. FDA has approved JAK inhibitors for the treatment of multiple autoimmune diseases including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and ulcerative colitis (Harrington et al., 2020; O'Shea, 2021; Troncone et al., 2020), and clinical trials are ongoing in other autoimmune diseases such as systemic sclerosis, Sjögren's disease, SLE, idiopathic inflammatory myopathies, alopecia areata, vitiligo, psoriasis,

Crohn's disease, spondyloarthritis/ankylosing spondylitis, and vasculitis (NIH, 2021). The JAK family comprises four different kinases (JAK1, JAK2, JAK3, tyrosine kinase 2) that may each be blocked somewhat selectively by different drugs. Different JAKs or combinations of JAKs are used by different cytokine receptors to mediate signaling, so JAK inhibitors may be used to block signaling through multiple different inflammatory cytokine receptors as appropriate for specific diseases. Additional drugs specifically targeting other inflammatory cytokines, including but not limited to IFN- $\gamma$ , IL-17, IL-23, and IL-12/23 shared subunit, are in use or in development for treating multiple different autoimmune diseases that share these specific inflammatory cytokines in the disease process (Baker and Isaacs, 2018).

Further studies to identify common immune pathways in different autoimmune diseases or subsets of different diseases will continue to provide insight into potentially targetable molecules that could lead to treatments for multiple different autoimmune diseases.

**Finding:** Specific mechanisms of immune-mediated damage that lead to the different clinical phenotypes share common immune pathways. Identifying specific proinflammatory signaling pathways and their cytokines as pathogenic in autoimmune diseases has yielded targeted therapeutics that aim to block their effects, as with, for example, TNF inhibitors and IL-1 inhibitors.

**Conclusion:** Continued research is needed to identify additional immune pathways that promote or inhibit autoimmune disease. Such pathways may be common to multiple autoimmune diseases and inform drug development.

### Animal Models

Animal models have played a critical role in defining common genetic and environmentally-induced mechanisms that drive the pathogenesis of autoimmune diseases as described in this chapter. Chapter 3 describes some of these animal models for the autoimmune diseases that are the focus of this report, but a detailed description of the many animal models investigators are using and the key findings and discoveries that studies using these models have produced is outside the scope of this report.

Existing animal models form a critical component of autoimmune disease research by providing mechanistic understanding of autoimmune diseases and preclinical data needed for translational research. For example, environmental causes of several human autoimmune diseases including celiac disease (Wu et al., 2021), rheumatic fever (de Loizaga and Beaton, 2021), and myocarditis (Boehmer et al., 2021) are known, and these

diseases could be used as models to accelerate identification of triggers and primary prevention for others. The ability to directly study effects of genetic modification, environmental effects, or potentially therapeutic immunomodulatory agents on the function of the immune system or the development of autoimmunity has been invaluable. Moreover, the ability to study immune cells and non-immune cells harvested directly from the target organs may provide a basis for subsequent studies in human tissues, which are often much less readily available or accessible. The committee wants to emphasize the importance of existing animal models that continue to provide valuable understanding of disease pathogenesis as well as the need to develop animal models for many autoimmune diseases where animal models do not currently exist and the need to continue to develop new animal models that answer specific and more translational research questions.

Future advances in tissue culture, such as 3D organoids, or organs-on-a-chip, which can model organs and systems such as the immune system (Park et al., 2020; Polini et al., 2019), as well as novel culture, animal, and other models, such as in silico confirmatory trials that use computer simulation to model virtual cohorts of patients (Pappalardo et al., 2019), may provide additional insight into autoimmune disease mechanisms or effective therapies.

**Finding:** Existing animal models are invaluable for studying mechanisms of autoimmune disease pathogenesis and providing preclinical data for translational research.

*Conclusion: Developing animal models for autoimmune diseases that currently have no models or are rare diseases and continuing to develop animal models that can better answer mechanistic questions posed by translational research would be of value. Technological innovation for the creation of new models for autoimmune disease research is needed.*

## MAXIMIZING ADVANCES IN TECHNOLOGY

Over the past decade, the availability of innovative technologies has completely changed the research environment and has come to dominate research on autoimmune diseases. These technological advances and the knowledge they have generated include the ability to perform more complex analyses of biological systems; knowledge about genomics and epigenomics; cytokine profiling; microbiomics, proteomics, metabolomics, and the study of changes in these “omics”; and generation of artificial intelligence. Fine-mapping genetic and epigenetic causal autoimmune disease variants, for example, enables researchers to identify clustering

among autoimmune diseases (Farh et al., 2015). As an example, a genetic region containing the gene for the enzyme tyrosine kinase 2 was identified in genome-wide association studies as linked to many autoimmune diseases, including psoriasis, SLE, and Crohn's disease (Makin, 2021). A disease-associated gene variant modifies the enzyme, which plays a role in cytokine function. Therapy to block enzyme function greatly reduced skin lesions in psoriasis, and a phase III trial in psoriasis and early-stage trials in Crohn's disease, SLE, and psoriatic arthritis are under way.

The ability to study gene expression profiles in immune cells at the single-cell level provides insights into the complex processes within heterogeneous tissue samples (Yofe et al., 2020). Moreover, combining the transcriptomics with proteomics on a single cell level (such as with flow or mass cytometry) can provide tremendous detail of complex subsets of immune and non-immune cells contributing to the inflammatory state within affected tissue. Analyses of synovial fluid from individuals with rheumatoid arthritis compared with non-autoimmune arthritis (osteoarthritis) combined single-cell RNA sequencing with mass cytometry and identified 18 unique cell populations—including different subsets of T cells, B cells, monocytes, and fibroblasts—and discovered the specific subsets expressing genes for key inflammatory cytokines IL-6 (expressed by fibroblasts) and IL-1b (expressed by pro-inflammatory monocytes) (Zhang et al., 2019). Another study utilizing mass cytometry coupled analyses from labial minor salivary gland biopsy samples with blood samples from individuals with Sjögren's disease to define immunophenotypes of cells from the affected organs and the peripheral blood (Mingueneau et al., 2016). The study identified different disease clusters based on profiles of cells within the affected tissue and peripheral blood including associations with disease activity parameters and potential pathogenic cells to be targeted therapeutically. In another study, single cell sequencing to define T-cell receptor gene expression to identify clones of T cells expanded within affected tissue samples of individuals with Sjögren's disease identified common T-cell receptor sequences within and between individual samples, strongly suggesting common antigen-driven immune response between different individuals (Joachims et al., 2016). The technologic advances afforded by single cell RNA sequencing provides a level of detail not possible through other measures to identify specific clonotypes of T cells in the absence of known antigens even from small samples such as cells isolated from biopsy specimens routinely obtained for diagnostic purposes. The analyses of such complex data sets are continually evolving, with recent study demonstrating the utility of latent factor modeling of single cell RNA sequencing data to define new pathways active in synovial tissues of individuals with rheumatoid arthritis and in the kidneys of individuals with SLE (Palla and Ferrero, 2020). Additional single

cell RNA sequencing studies have been performed in rheumatoid arthritis, SLE, systemic sclerosis, psoriatic arthritis, spondyloarthritis, Sjögren's disease, Kawasaki disease, multiple sclerosis, and type 1 diabetes (Kuret et al., 2021; Zhao et al., 2021). A possible avenue is to use high-throughput screening of thousands of autoantigens in parallel rather than single autoantigens or panels of single autoantigens. The continued development of new technologies and complex data-analysis methodologies will continue to gain unprecedented detailed knowledge of the immunopathologic processes in autoimmune diseases.

Gene-editing techniques are available to study the effects of insertion/deletion/alteration of genes of interest on immune cell function and disease models (Pavlovic et al., 2020). On a public health level, the use of these omics are being incorporated into defining the exposome, which will describe the effects of lifetime environmental exposures on health and disease (DeBord et al., 2016; Manrai et al., 2017).

Given the complexities of autoimmunity on multiple levels, researchers are using multi-omics approaches to provide a more comprehensive understanding of the immune response and the interplay between different components (cells, cytokines, genes, metabolism) (Chu et al., 2021). Such multi-omics approaches have demonstrated that distinct molecular clusters characterize individual systemic autoimmune diseases despite common clinical manifestations and that such clusters are similar across different systemic autoimmune diseases despite differences in clinical presentation (Barturen et al., 2021). These advanced technologies are generating datasets of increasing size and complexity, requiring more complex analyses that include systems modeling and machine learning, which have also advanced during this period and are providing additional insight into the complexities of autoimmune diseases (Brown et al., 2018).

Artificial intelligence (AI) and machine learning, for example, can be used to search electronic health records. An examination of electronic health records of 167,109 patients with rheumatoid arthritis found that the risk for lower-tract gastrointestinal perforation associated with treatment with tocilizumab and tofacitinib to be more than twice that of anti-TNF (Xie et al., 2016). These tools can be used for precision medicine, a term that encompasses determining disease treatment for individuals; prospective public health approaches that target disease prevention; and precision public health approaches to classify patients into at-risk or disease subsets for interventions (Conrad et al., 2020). In addition, genome-wide association studies match genetic variants to corresponding phenotypes in electronic health records to gain insight into outcomes and disease risk.

Regardless of the kind of data examined or the investigative purpose, the value of output depends on the rigor of the analytic methods used

to collect and interpret it. Big data analytics involves “integration of heterogeneous data, data quality control, analysis, modeling, interpretation and validation” (Ristevski and Chen, 2018), and the skill sets needed to fulfill these needs are essential to robust research. In addition, sound use of big data includes planning for optimum usability; in the case of electronic health records, for example, this would mean to share, clean, and archive data.

A multidisciplinary approach to longitudinal data collection in diverse population-based cohorts is needed in order to provide a strong foundation for integrated basic, translational, and clinical research necessary to address the complex and challenging questions relating to development, progression, and treatment of autoimmune diseases. Immunology, genetics, and clinical expertise in a variety of specialties including environmental health, epidemiology, and data science are among the disciplines needed to optimize the design, conduct, and analysis of this research. Existing and newly developed large data sets should apply rapid improvements in big data-analysis tools, including AI and machine learning, to advance knowledge in autoimmune diseases. For example, technical advances should be harnessed to increase information on subpopulations. Technologic tools could be used, among other things, to:

- examine genetic variation via genome-wide association studies;
- examine health disparities including the molecular underpinnings of differences in disease across race and ethnicity and how these might impact treatment;
- study environmental triggers for disease onset, disease flares, disease progression, and poor outcomes;
- elucidate immunophenotype immune cell pathways;
- identify metabolic pathways;
- decipher within and across disease-homogenous subsets; and
- compare persons with minimal disease or disease that has not yet manifested with those with severe disease or poor outcomes in order to expose key pathways to target in autoimmunity.

New and evolving technologies are supporting and advancing basic science, and translational research, to which the National Center for Advancing Translational Sciences is dedicated, is developing and using innovative technologies and methodologies to better search and interpret basic science findings in order to identify opportunities for enhancing diagnostics and therapeutics. The accruing knowledge will guide clinical research, from informing the types of samples collected and tests performed in observational studies to the design of intervention trials.

**Finding:** Advances in technology are rapidly providing novel insights into disease pathogenesis including autoimmune diseases. Multi-omics approaches are providing unique information about genetic and immune profiles that contribute to individual autoimmune diseases as well as revealing common pathogenic mechanisms between autoimmune diseases.

***Conclusion:** Continued development of innovative technologies will be important in providing breakthroughs in understanding mechanisms of autoimmune disease and may reveal new biomarkers that predict, diagnose, or prevent disease.*

## SUMMARY AND RESEARCH IMPLICATIONS

Characteristics that distinguish autoimmune diseases from each other and those that are common across autoimmune diseases provide valuable information about the pathogenesis of disease. These similarities and differences provide insights to better understand the epidemiology of disease, early predictors/biomarkers of disease, diagnosis, whether a disease is predicted to primarily affect an organ or have a systemic distribution, the occurrence of a flare, and the type of immune response that is important in driving disease, for example. The descriptions of common features across autoimmune diseases that this chapter provides lead to several research opportunities.

One implication of considering autoimmune diseases according to commonalities is that considering autoimmune diseases as a group according to common mechanisms of disease might provide novel insights beyond those gained by the more common approach that focuses on the affected organ or system. Examples of mechanistic themes that are common across autoimmune diseases that this chapter discusses include sex differences in incidence, severity, and type of immune response and the role of type I interferons in increasing autoimmune pathology (Barrat et al., 2019; Psarras et al., 2017). The current tendency of many researchers to focus on the organ or system may stem from the National Institutes of Health's (NIH's) organization of study sections based on that scheme. Animal models that better represent the clinical pathology and course of disease would enable studies that explore these common mechanisms. As a personalized medicine approach to health care (i.e., genomics/pharmacogenomics) becomes more common in medical practice, it becomes increasingly important to understand common mechanisms of autoimmune disease given that autoimmune disease may influence other coexisting inflammatory illnesses that are increasingly being considered as autoinflammatory diseases, including cardiovascular diseases such as

atherosclerosis. In addition, it is common for a patient with one autoimmune disease to have another autoimmune disease.

Many of the genes that confer susceptibility to autoimmune disease and that different autoimmune diseases share regulate the immune response, and some autoimmune diseases with very different clinical characteristics share genetic variants (Sogkas et al., 2021) (see Figure 4-1 and Figure 4-2). Fine-mapping genetic and epigenetic causal autoimmune disease variants can detect clustering among autoimmune diseases (Farh et al., 2015). Studying the function of genetic variant-related immune pathways will be critical to revealing the genotype–phenotype relationships that could provide targets for therapies. Polygenic risk scores are useful, but still have limitations, one being that the genomics data they are based on would likely need to include more diverse populations in order to be more broadly relevant.

The number and type of autoantibodies predict progression to autoimmune disease, but research is lacking in this area across autoimmune diseases. Insight can be gained by better characterizing autoantibodies that exist in many autoimmune diseases as well as those that are distinct for a particular disease and using those similarities and differences to better diagnose disease, predict the risk of developing an autoimmune disease, and predict the progression of disease. Cytokine profiles and microRNAs, for example, have demonstrated similar opportunities (Blanco-Domínguez et al., 2021; Idborg and Oke, 2021), and research on these and other novel biomarkers is called for.

For some autoimmune diseases, Black, Hispanic, and Indigenous people have an increased risk and greater severity of disease (Izmirly et al., 2021), while for other diseases, the highest risk occurs among White populations (Dabelea et al., 2014). Research pertaining to racial and ethnic patterns needs to fully address the spectrum of experiences represented by these findings, including living and work environments, social and economic factors, and a wide variety of stressors. To date, few studies focusing on race and ethnicity have used this lens.

Although sex differences in autoimmune diseases have been known and studied for some time, large gaps in defining sex and age differences and similarities remain. The field would benefit from research on sex differences in epidemiology, risk-factor identification and assessment, diagnostic criteria, coexisting illnesses, outcomes, and other topics. The committee emphasizes that sex differences need to be examined within the context of age because of the significant changes in sex hormone levels that occur across the lifespan in females and males. There is a gap in research across the lifespan for most autoimmune diseases.

An understanding of potential environmental causes of autoimmune diseases that is based on a systematic study of exposures including

dietary factors over time is needed to devise effective approaches to prevent and/or treat disease, including disease flares. Gene and environment interactions are also understudied. Twin concordance studies indicate the importance of both factors in contributing to autoimmune disease (Brix et al., 2001; Nistico et al., 2012; Ulff-Møller et al., 2018; Willer et al., 2003) research to better understand this relationship is needed. Current research indicates that environmental factors drive disease in individuals with genetic susceptibility (Bjornevik et al., 2022; Mehri et al., 2020; Robles-Matos et al., 2021; Vestergaard, 2002), yet the mechanisms behind the relationship remain unclear. It will be important to establish study sections that support research that examines interactions between genes and multiple environmental factors such as infections and chemicals. Currently an unintentional and artificial barrier exists, with grants for environmental topics going to the National Institute of Environmental Health Sciences, for example, and grants for infectious diseases going to the National Institute of Allergy and Infectious Diseases. This type of research may be important for efforts to develop effective intervention strategies to prevent development of disease in people who are at higher risk for developing disease.

Based on the known sex differences in disease for most autoimmune diseases and the well-described effect of sex hormones on immune cells and antibodies (Cook, 2008; Fischinger et al., 2019; Flanagan et al., 2017; Gubbels Bupp and Jorgensen, 2018; Regitz-Zagrosek et al., 2008), an area that lacks clinical and basic research studies includes the effect of exogenous hormone endocrine disruptors such as BPA and bisphenol S, which replaced BPA in plastic drinking bottles, on autoimmune disease. Also needed are studies on other hormone influencing factors such as those in diet—soy, for example—and medications such as birth control pills.

That research has linked several different infectious agents and chemicals to one autoimmune disease and one infectious agent to several different diseases suggests that common innate immune mechanisms are critical in driving disease. More research is needed to better characterize these common pathways across multiple autoimmune diseases clinically and through basic research. A better understanding of the mechanisms that occur commonly in many autoimmune diseases could fundamentally improve understanding of the pathogenesis of autoimmune disease and benefit patients with these conditions. Current technologies and methodologies such as multi-omics approaches, have already contributed greatly to this end, and continued development of innovative tools can support and drive further advances.

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## NIH Autoimmune Disease Research Efforts

### NIH OVERVIEW AND ORGANIZATIONAL STRUCTURE

Analyzing autoimmune disease research efforts at the National Institutes of Health (NIH) begins with an understanding of the funding, administrative structure, and authorities of NIH and its constituent parts. For more than 130 years, NIH has been the federal agency primarily responsible for sponsoring and conducting basic, clinical, and translational research (CRS, 2021); research training; and health information and dissemination in the United States. The agency is one of the 11 operating divisions in the U.S. Department of Health and Human Services (HHS).<sup>1</sup> The stated mission of NIH is to “seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability” (NIH, 2017a). From its origin as the single-room Laboratory of Hygiene in 1887, the agency now executes its missions and goals through the Office of the Director (OD) and 27 Institutes and Centers (ICs) that focus on different areas of biomedical research (CRS, 2019). Appendix E includes the full list of the ICs and their missions.

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<sup>1</sup> The other 11 operating divisions are: Administration for Children and Families, Administration for Community Living, Agency for Healthcare Research and Quality, Agency for Toxic Substances and Disease Registry, Center for Faith-Based and Neighborhood Partnerships, Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services, Food and Drug Administration, Health Resources and Services Administration, Indian Health Service, and Substance Abuse and Mental Health Services Administration (see HHS, 2022).

The OD sets policy and coordinates the programs and activities of all NIH components. Legislation in 2006 and 2016 resulted in a number of changes at NIH (CRS, 2019). The NIH Reform Act of 2006,<sup>2</sup> which implemented many recommendations from a National Academies of Sciences, Engineering, and Medicine report that reviewed the structure and organization of NIH, strengthened the OD to perform strategic planning, created a standardized reporting system, and provided funding (Common Fund) for NIH-wide initiatives (CRS, 2019; NRC, 2003). The Act also required an integrated biennial report of NIH research activities. In response to the Act, the OD established the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) in 2006 (DPCPSI, 2021). DPCPSI oversees a number of program Offices that coordinate research activities on specific topics that previously reported to the Director of NIH (DPCPSI, 2021). DPCPSI identifies and assists NIH in responding to emerging scientific opportunities, develops resources for the support of portfolio analyses and priority setting, and supports strategic planning, progress monitoring, evaluation, and reporting (CRS, 2019; DPCPSI, 2021).

More recently, the 21st Century Cures Act<sup>3</sup> directed the NIH Director to develop an NIH-wide strategic plan to expedite IC collaboration, provide guidance on investments made by NIH, and “leverage scientific opportunity, and advance biomedicine.” The first NIH-wide strategic plan covered fiscal year (FY) 2016 to 2020, and the most recent plan covers FY 2021 to 2025 (NIH, 2021d).<sup>4</sup> The Act also changed guidance on reporting on NIH research activities from the earlier mandated biennial report to a triennial report, the most recent of which covered FY 2016 to 2018.<sup>5</sup>

Congress annually appropriates funds for NIH overall and the ICs specifically, and sometimes Congress qualifies funds with specific requirements or instructions (NIH, 2021e). For example, Congress has required NIH to establish research programs, provided funding for research on specific topics, and mandated that NIH create research centers or institutes.

Today, NIH is the primary source of public funding for biomedical research in the United States with an annual discretionary budget authority of \$40.3 billion<sup>6</sup> for FY 2020 (NIH, 2020a; Viergever and Hendriks, 2016). Among federal agencies, NIH had the highest amount of discretionary funds in FY 2020 (Figure 5-1). Table 5-1 provides the trend in NIH appropriations from FY 2008 to 2020.

<sup>2</sup> National Institutes of Health Reform Act of 2006, Public Law 109-482, 109th Cong. (January 15, 2007).

<sup>3</sup> 21st Century Cures Act, Public Law 114-225, 109th Cong. (December 13, 2016).

<sup>4</sup> Available at: <https://www.nih.gov/about-nih/nih-wide-strategic-plan>, accessed November 29, 2021.

<sup>5</sup> Available at: <https://dpcpsi.nih.gov/oepr/nih-triennial-report>, accessed November 29, 2021.

<sup>6</sup> This includes \$80 million for Superfund Research activities (NIH, 2020a).



**FIGURE 5-1** Enacted HHS appropriations by agency (FY 2020).

NOTES: “Amounts in this figure are generally drawn from or calculated based on data contained in the explanatory statement accompanying the FY 2020 LHHS omnibus (P.L. 116-94), available in the Congressional Record, vol. 165, no. 204, December 17, 2019, pp. H11061-H11161. Enacted totals for FY 2020 do not include emergency-designated appropriations provided by P.L. 116-113, P.L. 116-123, P.L. 116-127, P.L. 116-136, or P.L. 116-139. For consistency with source materials, amounts in this figure generally do not reflect mandatory spending sequestration, where applicable, nor do they generally reflect transfers or reprogramming of funds pursuant to executive authorities.”<sup>1</sup>

ACF, Administration for Children and Families; ACL, Administration for Community Living; AHRQ, Agency for Healthcare Research and Quality; CDC, Centers for Disease Control and Prevention; CMS, Centers for Medicare and Medicaid Services; HRSA, Health Resources and Services Administration; SAMHSA, Substance Abuse and Mental Health Services Administration; OS, Office of the Secretary.

SOURCE: CRS, 2020.

<sup>1</sup> “Details may not add to totals due to rounding. The bar representing the combined mandatory and discretionary total for CMS has been abbreviated due to space constraints. When taking into account both mandatory and discretionary funding, CMS receives over 20 times the funding appropriated to either ACF or NIH in the FY 2019 LHHS omnibus. Amounts in this table (1) reflect all BA appropriated in the bill, regardless of the year in which funds become available (i.e., totals do not include advances from prior-year appropriations, but do include advances for subsequent years provided in this bill); (2) have generally not been adjusted to reflect scorekeeping; (3) comprise only those funds provided (or requested) for agencies and accounts subject to the jurisdiction of the LHHS subcommittees of the House and Senate appropriations committees; and (4) do not include appropriations that occur outside of appropriations bills.”

**TABLE 5-1** NIH Appropriations (FY 2008–2020)

FY	NIH Appropriations	Percent Change
2008	\$29,607,070,000	-
2009	\$30,545,098,000	3.2%
2010	\$31,238,000,000	2.3%
2011	\$30,916,345,000	-1.0%
2012	\$30,860,913,000	-0.2%
2013	\$29,315,822,000	-5.0%
2014	\$30,142,653,000	2.8%
2015	\$30,311,349,000	0.6%
2016	\$32,311,349,000	6.6%
2017	\$34,300,999,000	6.2%
2018	\$37,311,349,000	8.8%
2019	\$39,313,000,000	5.4%
2020	\$41,690,000,000	6.0%

NOTE: FY, Fiscal Year.

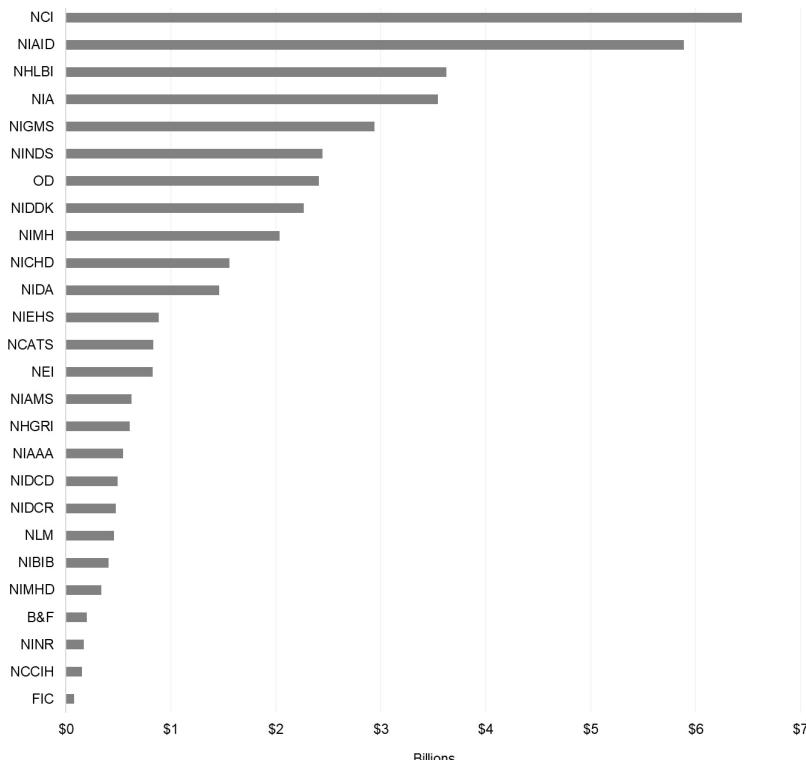
SOURCES: NIH, 2010, 2020b.

### Funding for NIH Institutes and Centers

NIH funding goes primarily to the ICs to support research conducted through both extramural grants and intramural research projects (NIH, 2020a). Extramural grants account for greater than 80 percent of NIH's funding, while intramural support accounts for about 11 percent of NIH funding (NIH, 2020a, 2021d, 2021e). In 2020, NIH awarded approximately 50,000 competitive grants to approximately 300,000 researchers (NIH, 2020a, 2021e).

NIH ICs have different missions that guide their activities, and may focus, for example, on a specific disease, organ system, life stage, field of science, or training or technology. The ICs also include the NIH Clinical Center, the National Library of Medicine, and the Center for Scientific Review (CSR).

ICs plan and manage their own research programs in coordination with the OD (NIH, 2021a, 2021e). ICs engage in strategic planning to set priorities and plan activities (NIH, 2015, 2021e). Figure 5-2 presents FY 2020 congressional appropriations for the ICs and OD. The variation in the level of appropriation is notable, with the National Cancer Institute (NCI) receiving the largest amount of funding and the Fogarty International Center receiving the smallest. The level of IC appropriation



**FIGURE 5-2** NIH Congressional appropriations by IC (FY 2020).

NOTE: B&F, Buildings and Facilities; FIC, Fogarty International Center; FY, Fiscal Year; IC, Institutes and Centers; NCATS, National Center for Advancing Translational Sciences; NCCIH, National Center for Complementary and Integrative Health; NCI, National Cancer Institute; NEI, National Eye Institute; NHGRI, National Human Research Institute; NHLBI, National Heart, Lung, and Blood Institute; NIA, National Institute on Aging; NIAAA, National Institute on Alcohol Abuse and Alcoholism; NIAID, National Institute of Allergy and Infectious Diseases; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIBIB, National Institute of Biomedical Imaging and Bioengineering; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIDA, National Institute on Drug Abuse; NIDCD, National Institute on Deafness and Other Communication Disorders; NIDCR, National Institute of Dental and Craniofacial Research; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS, National Institute of Environmental Health Sciences; NIGMS, National Institute of General Medical Sciences; NIMH, National Institute of Mental Health; NIMHD, National Institute on Minority Health and Health Disparities; NINDS, National Institute on Neurological Disorders and Stroke; NINR, National Institute of Nursing Research; NLM, National Library of Medicine; OD, Office of the Director.

SOURCE: NIH, 2021h.

correlates with the level of research, training, and other activities that the ICs that engage in these activities can support.

## NIH RESEARCH PROCESS

### Extramural Research Funding

At NIH, 24 of the 27 ICs fund the extramural research program (NIH Central Resource for Grants and Funding Information, 2020), which supports research across the United States and beyond (NIH, 2021d). Extramural research can be categorized generally as “unsolicited” investigator-initiated research or “solicited” targeted research (NIH Office of Extramural Research, 2021). Most applications submitted to NIH for research or research training, including fellowships, are investigator initiated (NIH Office of Extramural Research, 2021). Investigator-initiated opportunities may be attractive to new investigators owing to the freedom to create an application to pursue any area of science NIH supports without waiting for a particular funding announcement. Moreover, new investigators pursuing investigator-initiated research opportunities receive a higher pay line than established investigators, whereas there is no pay differential for new investigators pursuing solicited research opportunities (NIAID, 2016). All applications are submitted in response to Funding Opportunity Announcements (FOAs), which are publicly available documents in which NIH describes its intentions to make discretionary awards for which it selects the awardees and/or the amounts of funding via a competitive process.<sup>7</sup> FOAs can range from an NIH-wide umbrella announcement that channels investigator-initiated research applications, to a single IC’s announcement to solicit applications for a clearly defined scientific area in order to fulfill specific objectives<sup>8</sup> (NIH Office of Extramural Research, 2021). CSR is the entry point for all NIH grant, fellowship, and cooperative agreement applications (CSR, 2021; Hodge, 2021).

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<sup>7</sup> Non-discretionary awards, which are uncommon, are made to specific recipients, in accordance with statutory, eligibility, and compliance requirements. The award amount could be determined specifically or by formula (NIH Office of Extramural Research, 2021).

<sup>8</sup> The most common FOA types are as follows. Program Announcements (PAs) are statements about a new or ongoing activity or program that may also invite applications for grant support. Requests for applications (RFAs) solicit grant or cooperative agreement applications in a well-defined scientific area to accomplish specific program objectives. Parent Announcements are omnibus announcements that enable applicants to submit investigator-initiated applications. Notices of Special Interest (NOSI) highlight a topic of interest and direct applicants to one or more FOAs (often Parent Announcements) to submit applications for the initiative (NIH Office of Extramural Research, 2021).

CSR's Division of Receipt and Referral reviews grant applications for completeness and compliance with NIH policies and makes two referral assignments for each application (Hodge, 2021; NIH). The first assignment is to one or more NIH ICs for potential funding based on guidelines that each IC provides to CSR for assignment purposes, and these guidelines may include shared interests among different ICs (Hodge, 2021). The ICs' assignment guidelines are not available to the public (Hodge, 2021). The second assignment is to either a CSR review group, the case for 75 percent of applications, or to IC review groups associated with solicited FOAs (Murrin, 2019).

CSR scientific review groups, also called study sections, review the applications for scientific merit (CSR, 2020). Information on each study section, including its reviewers, topics covered, and overlap with related study sections, is available on the NIH website.<sup>9</sup>

There are two kinds of CSR study sections, chartered and special emphasis panels (CSR, 2020). Chartered, also called standing or recurring, study sections review most investigator-initiated research applications; the sections consist of members who are "primarily non-federal scientists with expertise in consist of scientific disciplines and current research areas" (NIH, 2018).

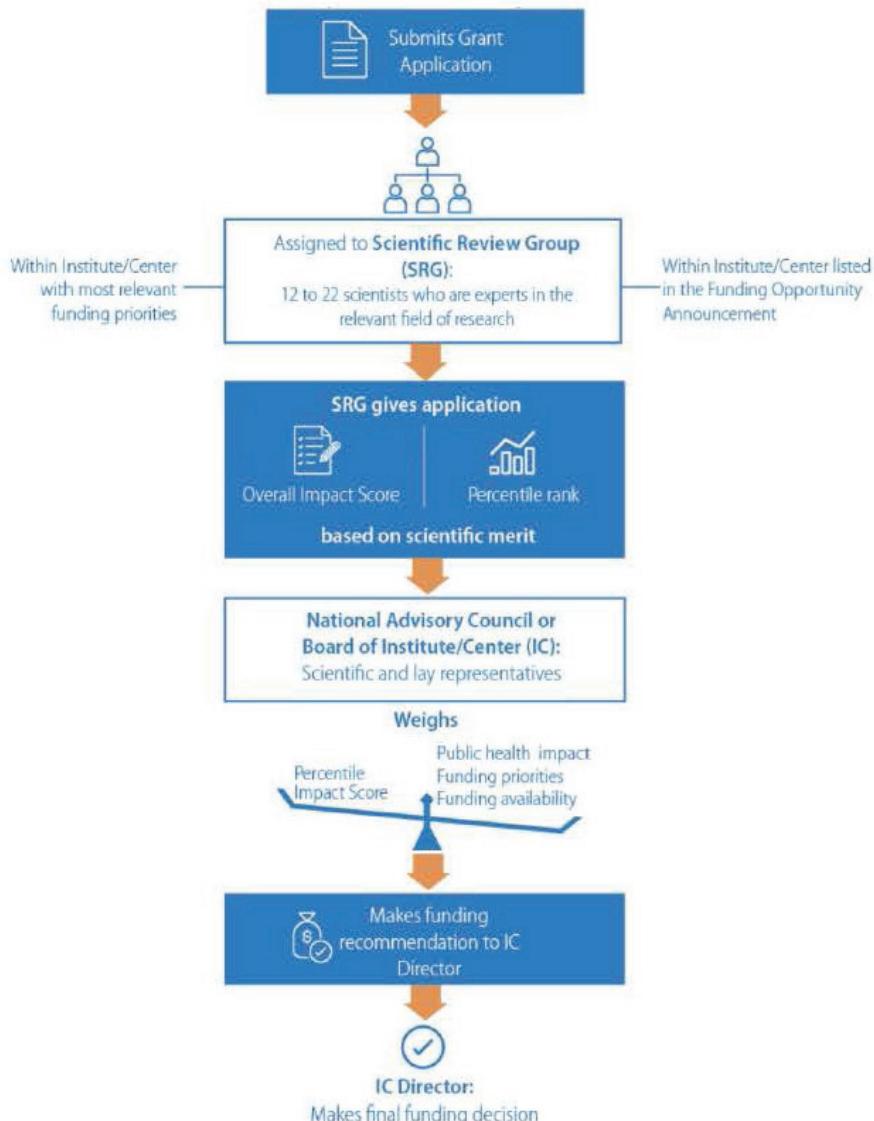
Special emphasis panels perform reviews when the subject matter does not match up with a study section, when assigning a project to an appropriate study section might create a conflict of interest, or in the case of certain types of applications such as fellowships, Small Business Innovation Research, and Small Business Technology Transfer Research applications (CSR, 2020; Hodge, 2021; NIH, 2013). A special emphasis panel consists of temporary members whom CSR recruits based on expertise needed for each meeting.

CSR assigns each application to a Scientific Review Officer (SRO) (NIH, 2013). An SRO is an extramural staff scientist who is the designated federal official responsible for ensuring an application meets peer-review requirements and for managing the review process (NIH, 2018; NIMH, 2021). The two-stage review process involves evaluation by a panel of primarily non-federal scientists, and approval by the IC Advisory Council/Board and the IC Director (NIH, 2018, 2019a).

In the first stage of review, assigned reviewers provide their preliminary assessments and critiques to the SRO, who uses them to plan and frame the session with the fully convened study section (CSR, 2020; NIH, 2018). The section chair and the SRO partner to run the study section review meeting (NIH, 2018). At the meeting, the assigned reviewers present a critique of the application, and members then discuss the application

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<sup>9</sup> Available at <https://public.csr.nih.gov/StudySections> (accessed November 19, 2021).



**FIGURE 5-3** NIH CSR review process.

NOTE: CSR, Center for Scientific Review; IC, Institute and Center; SRG, Scientific Review Group.

SOURCE: Adapted from figure developed by the Congressional Research Service (CRS, 2019) using information from NIH, 2016, 2018, 2019a.

in depth (Hodge, 2021; NIH, 2013, 2018). The members each provide a final overall impact score (Hodge, 2021; NIH, 2013, 2018).

In the second stage of review, the Advisory Council or Board of the assigned IC, comprising “both scientific and public representatives selected for their expertise, interest, or activity in matters related to health and disease,” makes funding recommendations based on the results of the study section’s review and the IC’s programs and priorities (Hodge, 2021; NIH, 2013, 2018) The directors of the ICs make the final funding decisions (NIH, 2018). Figure 5-3 depicts an overview of the process. Chapter 6 discusses CSR study sections that review applications that focus on autoimmune diseases.

The ICs use a similar process to review grant applications submitted in response to solicited FOAs, but they convene ad hoc special emphasis panels with expertise appropriate for each separate FOA (NIAID, 2020).

NIH uses a broad range of activity codes to categorize funding mechanisms for research activities. Extramural research activities are typically grants, contracts, or cooperative agreements (NIH, 2019b). Investigator-initiated research project grants, so-called R01 grants, are considered the traditional grant mechanism and constitute the largest single type of support NIH provides (NIH, 2021g). For the purpose of this study, the committee was also interested in fellowships, research career programs, training programs, and cooperative agreements. Table 5-2 provides a brief description of these grants.

### **Intramural Research Funding**

The NIH Intramural Research Program (IRP) supports research conducted on the NIH campuses, and 23 of the 27 ICs have an intramural component (IRP, 2021a; NIH, 2017b). Priority setting for intramural research projects is based on prior investigator success and innovative ideas, often in collaboration with investigators in other ICs or with extramural researchers.

The IRP budget supports more than 1,200 principal investigators and 4,000 postdoctoral fellows who conduct basic, translational, and clinical research (IRP, 2021b, 2021c). IRP principal investigators receive a review of their work every 4 years, and the external reviews are primarily retrospective (IRP, 2021a; Kastner, 2021; Rider, 2021). The IRP approach represents NIH’s commitment to individual researchers rather than individual projects, as is the case with extramural investigators, providing support for high-risk, high-reward projects not easily funded by R01 projects and for long-term studies requiring stable funding.

**TABLE 5-2** Select NIH Grant Types

Type of Grant	Category	Purpose
F	Fellowship Programs	"To provide individual research training opportunities (including international) to trainees at the undergraduate, graduate, and postdoctoral levels."
K	Research Center Programs	"To provide individual and institutional research training opportunities (including international) to trainees at the undergraduate, graduate, and postdoctoral levels."
P	Research Program Projects and Centers	"Program project/center grants are large, multi-project efforts that generally include a diverse array of research activities."
R	Research Projects	"These grants may be awarded to individuals at universities, medical and other health professional schools, colleges, hospitals, research institutes, for-profit organizations, and government institutions."
T	Training Programs	"To provide individual research training opportunities (including international) to trainees at the undergraduate, graduate, and postdoctoral levels."
U	Cooperative Agreements	A support mechanism frequently used for "high-priority research areas that require substantial involvement from NIH program or scientific staff."

SOURCE: NIH, 2019b.

### NIH Initiatives

NIH supports a number of specific initiatives. Initiatives originate in multiple ways, which include externally through congressional mandates, congressional language that is not a mandate, or direction from the Executive Branch (e.g., via HHS) as well as internally from the NIH OD, IC leadership and staff, or internal coordinating bodies. Directions from Congress or the Executive Branch are announced publicly, have specific goals, and may or may not have set-aside funding to support the goals. ICs may propose their own initiatives with or without dedicated funding. NIH initiatives may also derive from and be coupled with private-sector initiatives, with variable sharing of funds. Examples of the latter include large registries or clinical care consortia created by advocacy groups, strengthened in structure and resources by NIH or NIH-sponsored research, that pharmaceutical companies can use.

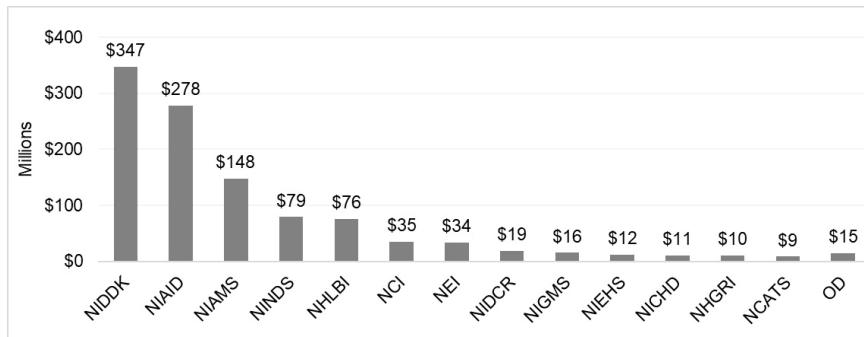
### Select NIH Autoimmune Disease Research Efforts

The previous discussion provided a brief overview of NIH funding and the process for awarding grants. The next section focuses more specifically on autoimmune disease research activities. For the purpose of this report and the timeframe available to the committee to conduct its work, the committee chose to limit its review to the OD and 13 NIH ICs—the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Arthritis and Musculoskeletal Diseases (NIAMS), National Institute on Neurological Disorders and Stroke (NINDS), National Heart, Lung, and Blood Institute (NHLBI), NCI, National Eye Institute (NEI), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of General Medical Sciences (NIGMS), National Institute of Environmental Health Sciences (NIEHS), *Eunice Kennedy Schriver* National Institute of Child Health and Human Development (NICHD), National Human Genome Research Institute (NHGRI), and National Center for Advancing Translational Sciences (NCATS)—that supported the majority of autoimmune disease research through intramural and extramural programs in FY 2020 based on the total amount of funding (see Figure 5-4).<sup>10</sup> Table 5-3 presents the general mission statements of the select NIH ICs. The committee notes that of these, the general mission of six Institutes focus on diseases, and six focus on organ systems or anatomy.

These ICs have different missions, favor different funding mechanism priorities, and focus on different autoimmune diseases. While they offer more detailed disease-specific interests in their website-searchable databases (Table 5-3), their reporting formats are not standardized, nor do they indicate how they choose diseases. Some listed diseases are common, such as rheumatoid arthritis, a focus of NIAMS, and some are exceedingly rare, such as autoimmune encephalitis, a focus of NINDS. Other diseases are lethal, such as vasculitis and systemic lupus erythematosus (SLE), which are areas of focus for NIAMS and NIDDK, while others are not lethal but cause life disruption treatable with today's technologies, such as Hashimoto's thyroiditis and Graves' disease, a focus of NIDDK. The complexity and diversity in the group of autoimmune diseases has contributed to how research and other efforts to understand the diseases are dispersed across NIH ICs, which in turn may lead to siloing of efforts if there are no systematic attempts to coordinate activities across NIH. Yet another perspective can be seen when considering a disease such as Sjögren's disease.

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<sup>10</sup> The committee notes that many investigators funded by NIH also receive support from philanthropy, industry, and other private-sector sources. The committee did not seek to quantify or outline the relative contributions of these other sectors.



**FIGURE 5-4** NIH autoimmune disease funding by IC (FY 2020).

NOTE: The 13 ICs and OD contributed approximately 97 percent of total autoimmune disease spending in FY 2020. NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIAID, National Institute of Allergy and Infectious Diseases; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NINDS, National Institute on Neurological Disorders and Stroke; NHLBI, National Heart, Lung, and Blood Institute; NCI, National Cancer Institute; NEI, National Eye Institute; NIDCR, National Institute of Dental and Craniofacial Research; NIGMS, National Institute of General Medical Sciences; NIEHS, National Institute of Environmental Health Sciences; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NHGRI, National Human Research Institute; NCATS, National Center for Advancing Translational Sciences; OD, Office of the Director.

SOURCE: NIH, 2021f.

Sjögren's disease is a prototypical, multisystemic autoimmune disease. Its manifestations include mucosal and ocular abnormalities, arthritis, respiratory and renal failure, multiple autoantibodies, cytopenias, neuropathy, maternal autoantibody-induced neonatal disease, and lymphadenopathy and lymphoma. Because it involves so many organ systems, Sjögren's disease does not have "a home" in NIH; NIAMS, NIAID, NEI, NINDS, NHLBI, NCI, NICHD, and NIDCR all can legitimately claim primary interest in grants focusing on this disease.

In an effort to categorize the autoimmune diseases relevant to the ICs in Table 5-3, the committee had to gather information from a variety of sources since such information was not readily available from a sole source. The committee relied on presentations by invited speakers from the ICs during the committee's information-gathering public sessions, publicly available information on the ICs' websites, and committee members' expert knowledge. The categorization of the ICs in Table 5-3, based on their mission statements and other publicly available information, reveals the broad and sometimes overlapping missions and focus areas

as they pertain to autoimmune diseases research. While there is some evidence of attempts to coordinate funding and research efforts among the ICs, it was difficult for the committee to assess how effective these efforts were, as discussed later in this chapter. Table 5-3 summarizes the autoimmune disease research focus of each IC, which range from basic to translational and clinical research.

### Strategic Planning for Autoimmune Disease Research at NIH

ICs engage in a strategic process to set research priorities. In an effort to understand whether and how the various ICs prioritize autoimmune diseases as part of their overarching institutional plans and vision planning, the committee reviewed the strategic plans for the 13 ICs that funded most of the autoimmune diseases work in FY 2020. The strategic plans offer insights into what the ICs consider to be the most pressing issues that they can tackle within their mission and vision, as well as those issues that will hold the most promise for advancing their respective fields. Complicating the committee's review of the strategic plans was the fact that there is no standardized approach and timeline by which the ICs release their reports (Table 5-4). Some ICs, such as NCI, release plans as part of the annual budget planning process to the President and Congress. Other Institutes—NIAMS, NIDDK, and NIGMS—release 5-year plans, while others—NHGRI, NIEHS, and NICHD—release reports periodically at intervals of 6 to 10 years. The committee found information about past reports to assess the frequency of the strategic planning process for some of the ICs, including NIAID, NHLBI, and NEI. This lack of standardization across ICs and consistency in the release of strategic plans for individual ICs has important implications since it may pose an obstacle for ICs in coordinating their strategic planning efforts, and subsequently, their funding and research efforts for autoimmune diseases. While the timeframe covered by some of the strategic plans overlap, the plans are at various stages of implementation.

Regarding the process for strategic planning, not all the ICs document their approach, so the committee was unable to fully evaluate how the ICs identified scientific and programmatic priorities outlined in the strategic plans. Some of the ICs, as discussed in the section below, go through a detailed process spanning 1 to 2 years that includes issuing a Request for Information (RFI) to solicit stakeholder feedback on their proposed themes or areas of focus. Broad and varied stakeholder input is essential for comprehensively surveying the field and ensuring that the priorities identified reflect what a variety of stakeholder groups consider as the most pressing issues.

**TABLE 5-3** Missions and Autoimmune Diseases of Focus of Select NIH ICs

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	Types of Research Supported for Autoimmune Diseases
<b>National Institute of Arthritis and Musculoskeletal Skin Diseases (NIAMS)</b>	"The mission of the NIAMS is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of basic and clinical scientists to carry out this research; and the dissemination of information on research progress in these diseases" (NIAMS, 2021b).	Rheumatic Diseases / Conditions (Systemic Lupus Erythematosus; Inflammatory Arthritis [Rheumatoid Arthritis; Ankylosing Spondylitis; and Psoriatic Arthritis]); Inflammatory Myopathies; Scleroderma; Sjögren's Syndrome; Antiphospholipid Syndrome; and Vasculitis (Giant Cell Arteritis, ANCA-Associated Vasculitis, Granulomatosis with Polyangiitis, and Behçet's disease); Skin Diseases / Conditions (Psoriasis, Pemphigus, Bullous Pemphigoid, Atopic Dermatitis [Eczema], Alopecia Areata, Vitiligo and Hidradenitis suppurativa); Autoinflammatory Syndromes (Tumor necrosis factor receptor-associated periodic fever syndrome [TRAPS], Cryopyrin-associated periodic syndromes [CAPS] and Systemic Juvenile Idiopathic Arthritis [sJIA]) (Mancini, 2021).	"Supports basic, translational, and clinical research, including clinical trials and observational studies, and mechanistic studies with a focus on mechanisms of disease"—basic immunology, inflammation, end-organ damage and repair; genomics, proteomics and other "Omics"; pain and fatigue; behavioral and biopsychosocial factors contributing to disease severity and quality of life and patient-reported outcomes; health disparities and special populations, e.g., pediatrics and pregnancy; training basic and clinical scientists to perform this research; and disseminating research and progress in these diseases (Mancini, 2021).

**TABLE 5-3** Continued

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	Types of Research Supported for Autoimmune Diseases
<b>National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)</b>	"The mission of the NIDDK is to conduct and support medical research and research training and to disseminate science-based information on diabetes and other endocrine and metabolic diseases; digestive diseases, nutritional disorders, and obesity; and kidney, urologic, and hematologic diseases, to improve people's health and quality of life" (NIDDK, 2021a; Spain, 2021).	Type 1 Diabetes; Crohn's Disease; Inflammatory Bowel Disease (IBD); Ulcerative colitis; SLE-Lupus Nephritis; Celiac Disease; Autoimmune Hepatitis; Autoimmune Thyroid diseases—Hashimoto's disease and Graves' disease; Autoimmune pancreatitis; and Glomerulonephritis—IgA and membranous; primary sclerosing cholangitis; and primary biliary cholangitis (Spain, 2021).	Invests in "a vigorous, investigator-initiated research portfolio that supports crosscutting science that can be broadly applied to many disease-specific research areas; supporting pivotal clinical studies and trials, with a focus on substantial participation of groups at highest risk; promoting a steady and diverse pool of talented new investigators; fostering exceptional research training and mentoring opportunities; and ensuring that science-based health information reaches patients, their families, health care providers, and the public through communications and outreach"

*continued*

**TABLE 5-3** Continued

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	Types of Research Supported for Autoimmune Diseases
<b>National Institute of Allergy and Infectious Diseases (NIAID)</b>	The mission of NIAID is “to conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic and allergic diseases (NIAID, 2017). NIAID has a unique mandate, which requires the Institute to respond to emerging public health threats” (Barron, 2021).	Type 1 Diabetes; Systemic Lupus Erythematosus; Rheumatoid Arthritis; Pemphigus; Vitiligo; Membranous Nephropathy; Scleroderma; Multiple Sclerosis; ANCA-associated vasculitis; Crohn’s disease; and IgG4-related disease; IBD; Autoimmune Lymphoproliferative Syndrome (ALPS); Autoimmune Polyendocrinopathy-Candidiasis-ectodermal Dystrophy (APECED); and Autoinflammatory Disease (Barron, 2021)	Supports research that investigates the role of the immune system, highlighting basic immune mechanisms; the role of the microbiome; the development of novel immune strategies to earlier detect, diagnose, treat and prevent disease; the application of knowledge of immune mechanisms to develop immunotherapies; and the use of improved animal models; and supports clinical trial networks and investigator-initiated clinical trials to evaluate immune-based treatment, such as cellular therapies, tolerance approaches, and other courses of action, each with integrated mechanistic studies (McNamara, 2021)

**TABLE 5-3** Continued

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	Types of Research Supported for Autoimmune Diseases
<b>National Institute of Neurological Disease and Stroke (NINDS)</b>	"The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease" (NINDS, 2020).	Multiple Sclerosis; Neuromyelitis Optica; MOG-Antibody associated disorders; Myasthenia Gravis; Guillain-Barré syndrome; Autoimmune encephalitis (i.e., Anti-N-methyl D-aspartate receptor); Transverse myelitis; Acute disseminated Encephalomyelitis; and Paraneoplastic syndromes (Utz, 2021)	Supports basic, translational, and clinical research; research that identifies gaps in research and public health needs; training a talented and diverse research workforce; supports the development of tools and resources to enable discoveries; and communicating and collaborating with all stakeholders, including the public (Utz, 2021)
<b>National Heart, Lung, and Blood Institute (NHLBI)</b>	"The mission of the NHLBI is to provide global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives" (NHLBI, 2014).	Vasculitis – Immune Thrombocytopenia; Autoimmune hemolytic anemia; Autoimmune thrombocytopenic purpura; coexisting diseases of systemic SLE (Atherosclerosis; Hypertension; Platelet activity); coexisting diseases of Rheumatoid Arthritis; and coexisting diseases of Scleroderma (Systemic Sclerosis, SSC), myocarditis (Kirby, 2021)	Supports basic, translational, and clinical research in the causes and coexisting diseases of autoimmune diseases

*continued*

**TABLE 5-3** Continued

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	Types of Research Supported for Autoimmune Diseases
<b>National Eye Institute (NEI)</b>	The mission of the NEI is to conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems of the blind (NEI, 2021a, 2021c).	Autoimmune uveitis; autoimmune retinopathy; autoimmune dry eye diseases (DED) including Sjögren's (NEI, 2021c)	Supports basic, translational, and clinical studies of the causes and mechanisms of autoimmune diseases of the eye. Ongoing projects include neuroretinal autoimmunity, ocular surface mucosal immunity, and the role of microbiota and their products in these contexts (NEI, 2020)

**TABLE 5-3** Continued

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	
<b>National Institute of Environmental Health Sciences (NIEHS)</b>	"The mission of the NIEHS is to discover how the environment affects people in order to promote healthier lives" (NIEHS, 2018; Rider, 2021).	Environmental triggers of autoimmune disease (NIEHS, 2021).	Invests in research to "advance research on environmental triggers of disease; foster training and development of young environmental health scientists and practitioners; enhance translation of knowledge from research to disease prevention; and develop improved safety assessment research on chemicals and other environmental factors" (NIEHS, 2020).

*continued*

**TABLE 5-3** Continued

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	Types of Research Supported for Autoimmune Diseases
<b>National Human Genome Research Institute (NHGRI)</b>	"As a leading authority in the field of genomics," the mission of NHGRI is "to accelerate scientific and medical breakthroughs that improve human health ... by driving cutting-edge research, developing new technologies, and studying the impact of genomics on society" (NHGRI, 2018).	Inflammatory diseases (Kastner, 2021)	Invests in research that evaluates genetic influences on the development of autoimmune and inflammatory diseases
<b>National Cancer Institute (NCI)</b>	The mission of NCI is "to lead, conduct, and support cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives" (NCI, 2018).		Supports research investigating the role of immunotherapy in the induction of autoimmune disease (e.g., checkpoint inhibitors) and immune regulation

**TABLE 5-3** Continued

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	Types of Research Supported for Autoimmune Diseases
<b>National Institute of General Medical Sciences (NIGMS)</b>	The mission of NIGMS mission is “to support fundamental biomedical research that increases understanding of life processes and lays the foundation for advances in disease diagnosis, treatment, and prevention” (NIGMS, 2018). “NIGMS-funded scientists investigate how living systems work at a range of levels, from molecules and cells to tissues, whole organisms, and populations. The Institute also supports research in certain clinical areas, primarily those that affect multiple organ systems. To assure the vitality and continued productivity of the research enterprise, NIGMS provides leadership in training the next generation of scientists, enhancing the diversity of the scientific workforce, reducing disparities, and developing research capacities throughout the country” (NIGMS, 2021).		Supports research investigating basic immunology and the regulation of T-cell immunity (NIGMS, 2018; NIH, 2021f)

*continued*

**TABLE 5-3** Continued

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	Types of Research Supported for Autoimmune Diseases
<b>National Institute of Dental and Craniofacial Research (NIDCR)</b>	The mission of “NIDCR is to advance fundamental knowledge about dental, oral, and craniofacial (DOC) health and disease and translate these findings into prevention, early detection, and treatment strategies that improve overall health for all individuals and communities across the lifespan” (NIDCR, 2021a).	Rheumatoid arthritis, Sjögren’s syndrome, lupus, and Psoriatic Spectrum Diseases (NIH et al., 2021b)	Supports basic, translational and clinical research, including mechanistic studies with a focus on mechanisms of disease—basic immunology, inflammation, and end-organ damage
<b>National Institute of Child Health and Human Development (NICHD)</b>	“The mission of the NICHD is to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all” (NICHD, 2019).		Supports research of immune tolerance in reproduction and immunoregulatory mechanisms (NICHD, 2020; NIH et al., 2021c)

**TABLE 5-3** Continued

IC Name	Mission	Autoimmune Diseases Relevant to Mission <sup>a</sup>	Types of Research Supported for Autoimmune Diseases
<b>National Center for Advancing Translational Sciences (NCATS)</b>	"The NCATS mission is to catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions" (NCATS, 2021a).		Supports translational research on autoimmune diseases, including support for the Rare Diseases Clinical Research Network consortia focusing on myesthenia gravis and vasculitis (Bamias et al., 2017)

<sup>a</sup>Disease lists are not intended to be comprehensive; sources included NIH websites and presentations delivered to the committee. A blank cell indicates that while the IC's mission may not focus on autoimmune diseases specifically, its research may benefit autoimmune disease research indirectly or may involve autoimmune diseases as a result of its broad mission.

**TABLE 5-4** Recent Strategic Plans Available from NIH ICs that Fund Autoimmune Disease Research

IC Name	Current Strategic Plan Years	Plan Period
NIAMS	FY 2020–2024	5 years
NIDDK	2021–2025	5 years
NIAID	2017	N/A
NINDS	FY 2021–2026	6 years
NHLBI	FY 2016	N/A
NEI	2021–2025	5 years
NIEHS	FY 2018–2023	6 years
NHGRI	2020 <sup>a</sup>	10 years <sup>b</sup>
NCI	FY 2023	1 year
NIGMS	2021–2025	5 years
NIDCR	2021–2026	6 years
NICHHD	2020	N/A
NCATS	2016	N/A

<sup>a</sup> The plan offers 10 bold predictions of what might be realized in human genomics by 2030 (Green et al., 2020).

<sup>b</sup> Based on schedule of previous plan.

NOTE: FY, Fiscal Year; IC, Institutes and Centers; NCATS, National Center for Advancing Translational Sciences; NCI, National Cancer Institute; NEI, National Eye Institute; NHGRI, National Human Genome Research Institute; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIDCR, National Institute of Dental and Craniofacial Research; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS, National Institute of Environmental Health Sciences; NIGMS, National Institute of General Medical Sciences; NINDS, National Institute on Neurological Disorders and Stroke.

SOURCE: Green et al., 2020; NCATS, 2016; NCI, 2021a; NEI, 2021b; NHLBI, 2016; NIAID, 2021b; NIAMS, 2020b; NICHHD, 2019; NIDCR, 2020; NIDDK, 2021b; NIEHS, 2018; NIGMS, 2021; NINDS, 2020.

The various strategic plans reference autoimmune diseases and issues of autoimmunity to varying degrees or not at all, as the discussion below notes for each individual IC. The Institutes that funded the most autoimmune diseases research and whose missions and focus align directly with autoimmune diseases—NIAMS, NIDDK, and NIAID—were more likely to mention the autoimmune diseases in their strategic plan. NIEHS, which is not a major funder of autoimmune diseases research, made mention of autoimmune diseases in its recent plan (FY 2018 to 2023) (NIEHS, 2018).

## NIAMS

The current NIAMS strategic plan covers FY 2020 to 2024 and includes a section on scientific objectives that are disease and tissue specific, one of which is to advance and speed systemic rheumatic and autoimmune diseases research, and crosscutting themes of focus for NIAMS. The cross-cutting scientific themes NIAMS identified acknowledge that most of the scientific challenges and opportunities transcend a single disease area or organ (NIAMS, 2020b). The four themes identified are all relevant to autoimmune diseases:

- **“Precision medicine for arthritis and musculoskeletal and skin diseases”** (NIAMS, 2020b). This involves, but is not limited to, leveraging new technologies and computational tools to improve knowledge of the molecular basis of health and disease.
- **“Shared mechanisms in health and among diseases.”** Focus areas include immunity and inflammation and the effects of environmental exposures.
- **“Patient-centric approaches to health and disease.”** Capturing patient-reported perspectives using tools such as the Patient-Reported Outcomes Measurement Information System (PROMIS®) as part of the research process.
- **“Health and disease in diverse populations.”** Promoting the relevance of NIAMS-funded research in groups that have been historically underrepresented in biomedical research in order to effect health equity for all populations.

The report also identifies aspirations or thematic issues that are germane to multiple diseases or conditions at NIAMS and those that hold the most promise for the future given the NIAMS portfolio (NIAMS, 2020b). The two most relevant for autoimmune diseases are:

- “Biomarkers will guide the choice of the most effective therapy for each individual rheumatoid arthritis patient [...and]
- “Preventive therapy will delay the onset of autoimmune diseases like lupus and rheumatoid arthritis” (NIAMS, 2020b).

Independently of its IC-specific strategic plans, NIAMS published the *Action Plan for Lupus Research* in 2015, intending that it supplement ongoing long-term plans as well as the work of the Lupus Federal Working Group (LFWG) and the Autoimmune Diseases Coordinating Committee (ADCC) (NIAMS, 2015). More information on these organizations appears later in this chapter.

## NIDDK

NIDDK established a Working Group of Council, consisting of 44 external scientists and patient advocates to provide input during the strategic planning process for its most recent strategic plan, which the Institute published in December 2021 (NIDDK, 2021b, 2021c). It issued an RFI in 2020 to seek input from different stakeholders, “including the scientific research community; patients and caregivers; health care providers and health advocacy organizations; scientific and professional organizations; federal agencies; and other stakeholders, including interested members of the public,” on the thematic considerations for the 5-year strategic plan (NIDDK, 2021b). After developing a draft strategic plan, NIDDK issued another RFI for the period August 10–31, 2021, to elicit feedback on the draft.

The strategic plan includes four major goals:

- “Advance understanding of biological pathways and environmental contributors to health and disease [...and]
- Advance pivotal clinical studies and trials for prevention, treatment, and cures in diverse populations [...and]
- Advance research to disseminate and implement evidence-based prevention strategies and treatments in clinics and community settings, to improve the health of more people, more rapidly and more effectively [...and]
- Advance stakeholder engagement — including patients and other participants as true partners in research” (NIDDK, 2021c).

## NIAID

The most recent NIAID-wide strategic plan is from 2017, and development of a new one is not yet scheduled.<sup>11</sup> The budget and planning page of NIAID’s website<sup>12</sup> does include strategic plans for various diseases and conditions and research areas, such as COVID-19, hepatitis B, tickborne disease research, vaccine adjuvants, and tuberculosis (NIAID, 2021b). NIAID’s last published strategic plan (NIAID, 2017) outlined the Institute’s then-current research priorities to inform its future decision making. The plan identified four scientific areas of focus, one of which is “allergy, immunology, and immune-mediated diseases,” including autoimmune disease. For this specific area, it emphasizes applying understanding of the human immune system in continuing to support immunology research that provides preclinical information that is crucial to

<sup>11</sup> Personal communication. Susan Cooper, M.Sc., Director, Office of Program Planning, Operations, and Scientific Information, NIAID, September 7, 2021.

<sup>12</sup> Available at <https://www.niaid.nih.gov/about/budget-planning>.

developing new strategies to diagnose, treat, and prevent infectious and immune-mediated diseases. Another area of emphasis involves supporting clinical trial networks committed to treating and preventing allergic and autoimmune diseases and to preventing graft rejection. A third and final area of emphasis identified for this scientific area involves determining the precise mechanisms of human immune regulation (NIAID, 2017).

### NINDS

NINDS organized its FY 2021 to 2026 strategic plan by focus areas that are not disease specific (NINDS, 2020). The four areas are:

- “Science: Support and perform rigorous and important neuroscience research.
- Training and Diversity: Fund and conduct neuroscience research training and career development programs to ensure a vibrant, talented, and diverse neuroscience workforce.
- Communications: Promote dynamic communication and diverse stakeholder engagement to accelerate scientific progress and reduce the burden of neurological disorders.
- Workforce Culture: Create and sustain a supportive work culture for the NINDS workforce that becomes the model for biomedical research and the neuroscience community” (NINDS, 2020).

While the strategic plan does not mention specific autoimmune diseases, NINDS seeks to advance research on the basic science and mechanisms of nervous system function in order to advance efforts to prevent and treat neurological disorders. In addition, NINDS will support the development and validation of biomarkers and outcome measures that are required to enable better and targeted therapeutic options for patients. The strategic plan also indicates as part of its science focus that it has a goal of supporting work to prevent neurological disorders and advance health equity (NINDS, 2020).

As part of its crosscutting strategies, the plan indicates NINDS’s intention to rely primarily on investigator-initiated research for its funded portfolio, but notes that productive collaborations and partnerships are essential as scientific advances highlight intersections between the interests of NINDS and other organizations (NINDS, 2020).

### NHLBI

The most recent strategic plan available for NHLBI is from 2016 (NHLBI, 2016). This report is organized according to 4 goals, 8 strategic

objectives, 132 research priorities, and 12 critical challenges, the latter of which the strategic plan defines as obstacles to scientific progress, which when overcome, will result in significant impact. The report's fifth strategic objective—developing and optimizing new diagnostic and therapeutic strategies to prevent, treat, and cure heart, lung, blood, and sleep diseases—states that one of its critical challenges is to understand the immune system from a systems biology perspective as a means of designing more efficacious treatment strategies for chronic inflammatory and autoimmune heart, lung, blood, and sleep diseases. This critical challenge was the only explicit reference to autoimmune diseases in the strategic plan. The critical challenges, along with a set of compelling questions, constitute NHLBI's strategic research priorities (NHLBI, 2016).

The NHLBI plan mentions that investigator-initiated projects will continue to be the Institute's primary focus, but it also acknowledges the importance of NHLBI-solicited research initiatives supported by new FOAs and that the plan's strategic research priorities will shape the development of future FOAs and other activities (NHLBI, 2016).

#### *NEI*

On November 1, 2021, NEI released a strategic plan for 2021 to 2025 (NEI, 2021b). This strategic plan is the ninth comprehensive plan for the Institute since it was established; the plan prior to the current plan was published in August 2012. The new plan has seven areas of emphasis within three research domains: "1) Visual system in health and diseases; 2) Capitalizing on emerging fields; and 3) Preventing vision loss and enhancing well-being" (NEI, 2021b). One of the focus areas within the first research domain is "immune system and eye health" (NEI, 2021b), which will address how NEI can develop crosscutting program priorities and overarching goals for ocular immunology, infection, and inflammation biology. As part of this goal, NEI's focus is to support research that develops targeted therapeutics for ocular immune-related diseases and improve imaging, biomarkers, and data analytics to support precision medicine for immune-mediated eye diseases, among other research goals. As with some of the other ICs, NEI points to how it leverages partnerships both within and outside of NIH to advance its mission and research priorities (NEI, 2021b).

#### *NIEHS*

The most recent version of the NIEHS strategic plan spans the years 2018 to 2023 and is organized around three themes:

- “Advancing environmental health sciences
- Promoting translation – data to knowledge to action
- Enhancing environmental health sciences through stewardship and support” (NIEHS, 2018).

Inflammation effects that result in autoimmune disorders is one major area of research interest identified for the first theme. In addition, NIEHS’s goals for advancing environmental health sciences include supporting research on the effects of the environment on biological systems and processes, which may have implications for many diseases, including autoimmune diseases (NIEHS, 2018).

#### NHGRI

NHGRI released its current strategic plan in 2020, following versions it issued in 2003 and 2011 (Green et al., 2020). In the plan, NHGRI identified four interrelated strategic areas that are at “the forefront of genomics” or are opportunities for human genomics in the next decade (Green et al., 2020). These areas are not disease specific, but overarching principles for genomics research that fall into the categories of:

- “Guiding principles and values for human genomics
- Sustaining and improving a robust foundation for genomics
- Breaking down barriers that impede progress in genomics
- Compelling genomics research projects in biomedicine” (Green et al., 2020).

While NHGRI funds and conducts some research on autoimmune diseases, its strategic vision does not mention them specifically (Green et al., 2020). It is conceivable that some of the details identified in the broad categories delineated above may have implications for several diseases, including autoimmune diseases.

#### NCI

NCI releases an institutional plan and budget annually for submission to the President and Congress. A summary document of the most current version, for FY 2023 (NCI, 2021a), highlights four focus areas: (1) clinical trials, (2) computer-based drug design, (3) precision prevention, and (4) tumor dynamics. The first highlighted area of the FY 2023 plan could have implications for autoimmune disease research in that a focus on expanding telemedicine into clinical trials could increase access to autoimmune disease trials in underserved communities. Similarly for

the third highlighted area, a focus on precision-medicine approaches to prevention could aid in developing personalized prevention approaches for autoimmune diseases based on genetics, family history, environmental exposures, and behaviors.

The FY 2022 summary document (NCI, 2021b) highlighted four focus areas including “cancer drug resistance, molecular diagnostics for cancer treatment, obesity and cancer, and cancer survivorship.” The FY 2021 plan summary (NCI, 2019a) identified three opportunities in cancer research: “the immune system and microbiome, artificial intelligence, and implementation science.” The FY 2021 plan’s first area of research, which focuses on harnessing the immune system in the development of immunotherapies, may have implications for individuals with autoimmune diseases, as trials for existing immunotherapies have excluded these individuals (NCI, 2019b).

#### *NIGMS*

NIGMS released its current strategic plan in 2021. True to NIGMS’s mission, which is crosscutting in nature to support biomedical research in general, the plan (NIGMS, 2021) is organized around five goals that include sustaining support for investigator-initiated research and investing in developing a skilled and diverse biomedical research workforce. NIGMS has supported some autoimmune diseases-focused research, so its goals may have relevance for the field of autoimmune diseases.

#### *NIDCR*

NIDCR released an RFI in August 2019 to solicit stakeholder input for its 2020 to 2025 strategic plan, but decided to postpone the plan release following the retirement of the former director in December 2019 and pending the installation of a new director who would provide new leadership and direction for the Institute (NIDCR, 2021b). The FY 2021–2026 strategic plan will be organized around five priority areas, all of which could potentially have a bearing on autoimmune diseases, such as SLE and Sjögren’s disease, that involve dental, oral, and craniofacial (DOC) diseases (NIDCR, 2021b). These include:

- “Advancing cross-disciplinary fundamental research in the biomedical, behavioral, social, and environmental sciences and driving translation toward early diagnosis, prevention, and treatment of DOC diseases and conditions across the lifespan.
- Developing more precise and individualized ways of managing and preventing DOC diseases.

- Accelerating research translation and the uptake of new discoveries into oral and general healthcare practices that reduce health inequities and disparities and improve oral health outcomes for individuals and communities worldwide.
- Nurture future generations of DOC researchers and oral health professional scholars who can address existing and emerging challenges driven by personalized and public health needs and a continually evolving landscape of science and technology advances.
- Expanding existing partnerships and create new ones to advance the NIDCR research enterprise and increase its reach and impact" (NIDCR, 2021b).

### *NICHD*

NICHD's most recent strategic plan is for the year 2020, having released its previous two strategic plans in 2000 and 2012. The report is organized around five themes, which include an emphasis on understanding the biological basis of development; promoting gynecologic, andrologic, and reproductive health; promoting healthy pregnancies and lifelong wellness; improving the health of children and adolescents as they transition into adulthood; and safe, effective therapies and devices for pregnant women, children, and individuals with disabilities. While the strategic plan does not focus on specific diseases or conditions, the plan mentions how the results from NICHD-funded researchers working with maternal mouse models that showed the persistence of fetal cells post-delivery could offer insight into diseases that affect women, including autoimmune diseases (NICHD, 2019).

### *NCATS*

NCATS was established in 2011 and has published a strategic plan from 2016 (NCATS, 2016). The Center's research is not disease specific but rather focuses on disease commonalities and the translational process. The NCATS strategic plan is organized around four strategies, and the first, and most relevant for autoimmune diseases, is to conduct and support innovative research to reveal fundamental scientific and operational principles of translational science to drive the development and dissemination of novel medical interventions. Among several objectives listed to support this strategy are (1) "to identify biological commonalities among diseases and use insight into shared mechanisms and pathways to test and treat multiple human diseases and conditions" (NCATS, 2016), and (2) to "drive development of medical interventions for rare diseases that

lack safe and effective treatments” (NCATS, 2016). The plan also points out obstacles that can limit the progress of translational science such as a lack of data interoperability; “a shortage of qualified biomarkers to diagnose disease and measure treatment response”; and “inadequate development and measurement of appropriate clinical outcome measures or endpoints, including patient-reported outcomes.” While no diseases are named in the plan, translational science research could benefit the field of autoimmune diseases (NCATS, 2016).

In summary, the committee notes the inherent difficulty in assessing the priorities of the ICs as it pertains to autoimmune diseases (as discussed earlier in this chapter). While ICs develop their strategic plans independently, on different schedules, and focus on broad thematic issues, there are sufficient commonalities in the themes and priority areas highlighted across the strategic plans that the committee reviewed to indicate that the process could benefit from a concerted effort. For example, some of the ICs, such as NIAMS and NEI, highlighted the development of biomarkers that will aid in the delivery of precision medicine. NIAID, NIAMS, and NIEHS all prioritized additional research on the basic science and mechanisms of the human immune system, and NIAMS also mentions the importance of understanding the effects of environmental exposures, which is a shared goal with NIEHS. Beyond scientific issues, a few of the ICs, such as NIDDK and NIAMS, highlight other priority areas such as the importance of the patient as partner in the research process, and NIAMS and NCATS call for the use of patient-reported outcomes in research. Better coordination in strategic planning and priority setting efforts across the ICs could enable the ICs to harness their expertise and resources effectively to address the pressing issues in autoimmune diseases research.

## CONGRESSIONAL ACTIONS AND NIH AUTOIMMUNE DISEASE RESEARCH

On numerous occasions, Congress has issued mandates pertaining to autoimmune disease research at NIH. Constituents, advocacy groups, and other stakeholders who request congressional action on autoimmune diseases research have contributed greatly to such action, often through organized advocacy efforts (Autoimmune Association, 2021; Keenan, 2020). These mandates provide direction and in some cases funding for specific activities NIH-wide or at the IC level. This section provides an illustrative selection of specific mandates.

The National Institutes of Health Revitalization Act of 1993<sup>13</sup> directed multiple ICs to pursue research on specific autoimmune diseases. The

<sup>13</sup> National Institutes of Health Revitalization Act of 1993, Public Law 103-43, 103rd Cong., 1st sess. (June 10, 1993).

Act tasked NIAMS to develop a plan to expand research into etiology, prevention, diagnosis, treatment, and rehabilitation of arthritis affecting children; to establish a disease center for this purpose; and to make recommendations for expanding funding for such research. The Act encouraged NIAID to collaborate with external entities to research chronic fatigue syndrome, issue research grants to study it, establish an extramural study section to review related research, appoint experts on the disease to appropriate NIH advisory committees and boards, and report on NIH's work and priorities involving the disease. The Act also enabled NEI to issue grants to support a variety of basic and clinical research on diabetes and the eye and to improve patient care. Furthermore, the Act directed NINDS to conduct and support research on multiple sclerosis, particularly the effects of genetics and hormonal changes on disease progression. Congress did not include appropriations language for these efforts.

One directive that has been renewed over many years is the Special Statutory Funding Program for Type 1 Diabetes Research, or Special Diabetes Program, a special appropriation for research on type 1 diabetes that NIDDK administers on behalf of the HHS Secretary in collaboration with multiple ICs and the Centers for Disease Control and Prevention (CDC) and with input from the Diabetes Mellitus Interagency Coordinating Committee. Begun in 1998, the Special Diabetes Program established collaborative research consortia and clinical trials networks dedicated to preventing, treating, and curing type 1 diabetes. Annual funding for the program has grown over time from \$30 million to the current level of \$150 million.<sup>14</sup>

The Children's Health Act of 2000<sup>15</sup> called for the NIH Director to "expand, intensify, and coordinate research and other activities involving autoimmune diseases among the institutes." It also requested establishing an Autoimmune Diseases Coordinating Committee (ADCC) to coordinate activities across NIH and with other federal health programs. Its members would include representatives of germane NIH ICs, federal departments, and agencies, including CDC and the Food and Drug Administration (FDA). The ADCC was to create a plan for "conducting and supporting a broad range of research and education activities relating to biomedical, psychosocial, and rehabilitative issues, including studies of the disproportionate impact of such diseases on women." It was to determine NIH priorities for autoimmune diseases, which would "reflect input from a broad range of scientists, patients, and advocacy groups." Planning was to include research to identify the reasons for the incidence and prevalence

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<sup>14</sup> Consolidated Appropriations Act, 2021, Public Law 116-260, 116th Cong. 2nd sess. (December 27, 2020).

<sup>15</sup> Children's Health Act of 2000, Public Law 106-310, 106th Cong. 2nd sess. (October 17, 2000).

of the diseases; basic research of causes; epidemiologic studies on disease frequency and progression, including disparities among sexes and racial and ethnic groups; improvement of screening techniques; and clinical research to develop treatments. The ADCC was also to plan information and education programs for the public and medical community. The ADCC would issue reports to Congress on autoimmune disease-related activities conducted or supported by NIH and the cost of NIH activities for each disease, and would identify appropriate future projects for consideration by NIH or other research entities. Congress authorized appropriations for FY 2001 through 2005, but the language did not include amounts.

The Children's Health Act of 2000 also asked NIAMS and NIAID to expand and intensify programs for research and other activities involving juvenile arthritis and related conditions. Congress authorized NIAMS and NIAID to be appropriated "such sums as may be necessary" for FY 2001 through FY 2005. In addition, the Act directed NIDDK to conduct or support long-term epidemiology studies in those who have or who are at risk for type 1 diabetes in order examine the causes, characteristics, and complications of the disease, and to undertake an effort to support regional clinical research centers for preventing, detecting, treating, and curing juvenile arthritis and related conditions. NIH was to join HHS in a national effort to increase "research and development of prevention strategies, including consideration of vaccine development, coupled with appropriate ability to evaluate the effectiveness of such strategies in large clinical trials of children and young adults." NIDDK was to be appropriated sums for FY 2001 through 2005, but the Act did not specify what those sums should be.

Another statute Congress passed in 2000 was the Public Health Improvement Act,<sup>16</sup> which included directives to extend and intensify the study of SLE and charged NIAMS with coordinating with other ICs doing work related to SLE. NIAMS was asked to conduct or support research to include investigating the reasons for the preponderance of SLE in women, including African American women; basic research on disease causes; epidemiologic studies to examine disease progression, its frequency, and difference between sexes and racial and ethnic groups; development of improved diagnostic techniques; and clinical research to develop and evaluate new treatments. The Act also directed NIAMS to develop information and education programs for the health care community and the public. It was authorized appropriations for FY 2001 through 2003, but the Act did not specify sums.

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<sup>16</sup> *Public Health Improvement Act*, Public Law 106-505, 106th Cong., 2nd sess. (November 13, 2000).

Congress enacted the Rare Diseases Act of 2002<sup>17</sup> with the intent of increasing the study of rare diseases and disorders—"defined as those affecting fewer than 200,000 individuals in the United States"—and the Act includes Crohn's disease as an example of a rare disease. NIH created the Office of Rare Diseases in 1993, but it lacked statutory authorization, so the Act requested that NIH establish the Office within the OD. The Act directed the Office to recommend a varied research and educational agenda and to promote coordination and cooperation across the NIH ICs and those they supported, and, in collaboration with directors of other ICs, it was enabled to make cooperative agreements and to award grants to regional centers of excellence on rare diseases. Other duties specified for the Office included promoting the establishment of an information clearinghouse on rare and genetic diseases for the public and medical community, liaising with national and international organizations, reporting biennially on the activities that had and should occur, and reporting annually to Congress. The Office was appropriated "such sums as already have been appropriated for FY 2002, and \$4,000,000 for each of the FY 2003 through 2006" for the purpose of cooperative agreements or grants for the regional centers of excellence for rare diseases.

Congress enacted the Pancreatic Islet Cell Transplantation Act of 2004<sup>18</sup> to "increase the supply of pancreatic islet cells for research, to provide for better coordination of Federal efforts and information on islet cell transplantation." Annual reports prepared by the NIDDK-led Diabetes Mellitus Interagency Coordinating Committee were directed to evaluate the federal activities and programs related to pancreatic islet transplantation and research, recommend legislation to increase the supply of pancreas tissue for islet cell transplantation, and address the adequacy of federal funding. The Act did not provide funding authorization or appropriation amounts.

The American Recovery and Reinvestment Act of 2009<sup>19</sup> was a fiscal stimulus package developed in response to the Great Recession. Of the money appropriated to NIH, \$7,400,000,000 was transferred to the ICs and the Common Fund,<sup>20</sup> in proportion to the appropriations otherwise made to them for FY 2009. The funds were to be used to "support additional scientific research," and money was to be consolidated with and used for

<sup>17</sup> *Rare Diseases Act of 2002*, Public Law 107-280, 107th Cong., 2nd sess. (November 6, 2002).

<sup>18</sup> *Pancreatic Islet Cell Transplantation Act of 2004*, Public Law 108-362, 108th Cong., 2nd sess. (October 25, 2004).

<sup>19</sup> *American Recovery and Reinvestment Act of 2009*, Public Law 111-5, 111th Cong., 1st sess. (February 17, 2009).

<sup>20</sup> Not included among the recipients were the National Institutes of Health—Buildings and Facilities, the Center for Scientific Review, the Center for Information Technology, the Clinical Center, and the Global Fund for HIV/AIDS, Tuberculosis and Malaria.

“the same purposes as the appropriation or fund to which [it] was transferred.” In addition, \$1,800,000,000 was appropriated to NIH for repair, renovation, and construction of non-federal and NIH facilities and for instrumentation and research equipment.

The 21st Century Cures Act,<sup>21</sup> enacted in 2016 to expedite the discovery, development, and delivery of new treatment and cures, appropriated \$4.8 billion to biomedical research. While autoimmune disease research was not specifically named in the Act, the crosscutting nature of autoimmune disease research could enable it to benefit from the funding designated for NIH initiatives such as the NIH Beau Biden Cancer Moonshot, the Brain Research Through Advancing Innovative Neurotechnologies<sup>®</sup> (BRAIN) Initiative, and the Precision Medicine Initiative. In addition, funding was directed to the Next Generation of Researchers Initiative to help support new researchers, sustain research careers, and promote growth, stability, and diversity of the biomedical research workforce.

In 2018, the National Clinical Care Commission Act<sup>22</sup> established an HHS Commission, which included NIH as a member, to evaluate and make recommendations on how to better leverage and coordinate federal programs related to as many as two metabolic or autoimmune diseases with insulin-related etiology. In making its recommendations, the Act instructed the Commission to consider preventing and reducing the diseases and complications, “gaps in Federal efforts to support clinicians in providing integrated high-quality care,” “improvement in and improved coordination of Federal education and awareness activities related to the prevention and treatment of the diseases,” methods for dissemination of educational materials, and opportunities for consolidating overlap in federal programs related to the diseases. The Commission was to submit an operating plan, which could include a budget for the Commission’s activities, and a final report to the HHS Secretary and Congress, and it decided to focus on type 1 and type 2 diabetes. Congress did not appropriate funds for the Commission’s operation, and an HHS Joint Funding Agreement supported the Commission’s activities (National Clinical Care Commission, 2018).

#### *Relevant Bills or Resolutions That Did Not Pass*

There have been congressional actions directed to NIH autoimmune disease research efforts that Congress did not pass into law. One example is a bill that members of Congress submitted twice—the NIH Office of

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<sup>21</sup> 21st Century Cures Act, Public Law 114-255, 114th Cong., 2nd sess. (December 13, 2016).

<sup>22</sup> National Clinical Care Commission Act, Public Law 115-80, 115th Cong., 1st sess. (November 2, 2017).

Autoimmune Diseases Acts of 1998<sup>23</sup> and 1999<sup>24</sup>—which called for establishing an Office of Autoimmune Diseases in the NIH OD. The 1999 bill (see Appendix F) was introduced by then Senator Joseph Biden. According to that proposed bill, the Director of the Office, consulting with the ADCC, was to recommend an agenda for autoimmune disease research across the ICs. The Director of the Office was also to promote coordination and cooperation among the ICs involved in autoimmune disease research and those supported by their research; promote NIH allocation of resources for such research; annually report on the research, including identifying projects that should be conducted or supported; and serve as the principal advisor to HHS, NIH, CDC, and FDA and other agencies regarding autoimmune diseases. The 1999 bill authorized a FY 2000 appropriation of \$950,000 (20 percent more than that of the 1998 bill) as well as “such sums necessary for fiscal years 2001 and 2002.” While both bills required establishing or operating the ADCC, and the ADCC had been formed by the time of the 1999 bill, the establishment and duties of the ADCC were not required by statute until The Children’s Health Act of 2000. In the 2000 Act, the ADCC was directed to carry out certain duties that had been outlined for the proposed NIH Office of Autoimmune Diseases.

Other select examples of congressional action are the Scleroderma Research and Awareness Act (Congresses of 2009–2010, 2011–2012, and 2013–2014)<sup>25,26,27</sup> requesting the director of NIAMS to “expand, intensify, and coordinate” research of the disease; the Psoriasis and Psoriatic Arthritis Research, Cure, and Care Act of 2007,<sup>28</sup> 2009,<sup>29</sup> and 2011,<sup>30</sup> which encouraged the Director of NIH to “explore the development of a virtual Center of Excellence for Collaborative Discovery in Psoriasis and Comorbid Research or some other mechanism through which public and private

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<sup>23</sup> NIH Office of Autoimmune Diseases Act of 1998, HR 4873, 105th Cong., 2nd sess., Congressional Record 144, no. 150, daily ed. (October 20, 1998); H 11695.

<sup>24</sup> NIH Office of Autoimmune Diseases Act of 1999, S 1897, 106th Cong., 1st sess., Congressional Record 145, no. 157, daily ed. (November 9, 1999); S 14407.

<sup>25</sup> Scleroderma Research and Awareness Act of 2010, HR 2408, 111th Cong., 1st sess., Congressional Record 155, no. 74, daily ed. (May 14, 2009); H 5664.

<sup>26</sup> Scleroderma Research and Awareness Act of 2011, HR 1672, 112th Cong., 1st sess., Congressional Record 157, no. 57, daily ed. (May 2, 2011); H 2933.

<sup>27</sup> Scleroderma Research and Awareness Act, S 1239, 113th Cong., 1st session, Congressional Record 159, no. 94, daily ed. (June 27, 2013) S 5498.

<sup>28</sup> Psoriasis and Psoriatic Arthritis Research, Cure, and Care Act of 2007, HR 1188, 110th Cong., 1st sess., Congressional Record 153, no. 30, daily ed. (February 16, 2007); H 1895.

<sup>29</sup> Psoriasis and Psoriatic Arthritis Research, Cure, and Care Act of 2009, HR 930, 111th Cong., 1st sess., Congressional Record 155, no. 27, daily ed. (February 10, 2009); H 1156.

<sup>30</sup> Psoriasis and Psoriatic Arthritis Research, Cure, and Care Act of 2011, S 1107, 112th Cong., 1st sess., Congressional Record 157, no. 74, daily ed. (May 26, 2011); S 3427.

sector findings regarding psoriasis and its comorbid conditions can be regularly shared and leveraged"; the Prevention, Awareness, and Research of Autoimmune Disease Act of 2006<sup>31</sup> (as well as during the 2003–2004 Congress<sup>32</sup>), which required NIEHS to award grants to research environmental triggers of autoimmune diseases in genetically predisposed people; and the Women's Autoimmune Diseases Research and Prevention Act (Congresses of 2001–2002<sup>33</sup> and 2003–2004<sup>34</sup>), which directed the ADCC to include research on the causes of autoimmune diseases in women, particularly genetic, hormonal, and environmental factors; development of information and education programs on risk factors, including hormonal and environmental factors; and community outreach to historically underserved populations of women in its plan for NIH activities.

## CURRENT COORDINATION OF AUTOIMMUNE DISEASE RESEARCH AT NIH

### Role and Function of the Autoimmune Diseases Coordinating Committee

NIH established the ADCC in 1998 in response to congressional interest in the autoimmune diseases and the need to coordinate activities across the ICs and with other federal health programs and activities for autoimmune diseases (ADCC, 2000).<sup>35</sup> The inaugural ADCC membership consisted of representatives of the ICs that are engaged in autoimmune diseases research, and members from other federal departments and agencies that focus on autoimmune diseases, such as CDC, Veterans Administration, and FDA.<sup>36</sup> In addition, although Congress did not require it, the ADCC extended membership invitations to advocacy

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<sup>31</sup> *Prevention, Awareness, and Research of Autoimmune Disease Act of 2006*, HR 6214, 109th Cong., 2nd sess., Congressional Record 152, no. 123, daily ed. (September 27, 2006); H 7674.

<sup>32</sup> *Prevention, Awareness, and Research of Autoimmune Disease Act*, HR 3359, 108th Cong., 1st sess., Congressional Record 149, no. 148, daily ed. (October 21, 2003); H 9811.

<sup>33</sup> *Women's Autoimmune Diseases Research and Prevention Act*, HR 5104, 107th Cong., 2nd sess., Congressional Record 148, no. 93, daily ed. (July 11, 2002); H 4552.

<sup>34</sup> *Women's Autoimmune Diseases Research and Prevention Act*, HR 370, 108th Cong., 1st sess., Congressional Record 149, no. 14, daily ed. (January 27, 2003); H 170.

<sup>35</sup> *Children's Health Act of 2000*, Public Law 106–310, 106th Cong. (October 17, 2000), H.R. 4365. *Departments of Labor, Health and Human Services, And Education, And Related Agencies Appropriation Bill, 1998*, HR 105–205, 105th Cong., 1st sess. (July 25, 1997).

*Departments of Labor, Health and Human Services, And Education And Related Agencies Appropriation Bill, 1998*, 105th Cong., 1st sess. (July 24, 1997); Senate Report 105–58.

<sup>36</sup> *Children's Health Act of 2000*, Public Law 106–310, 106th Cong., 2nd sess. (October 17, 2000), H.R. 4365.

groups and representatives from private autoimmune disease organizations.<sup>37</sup> The current membership of the ADCC remains similar, and the membership of advocacy groups has only continued to grow, providing these stakeholders with a greater voice (NIAID, 2021a). NIAID is the current chair of the ADCC.

In the first 2 years of its existence, the ADCC had several major accomplishments, as documented in its first report released in 2000 (ADCC, 2000). The committee analyzed information on autoimmune diseases research funding and research at NIH and established multi-IC collaborative working groups for autoimmune diseases. The ADCC was also instrumental in enhancing coordination and facilitating private and public partnerships for autoimmune disease research both within the ICs and with private disease organizations. In FY 1999, NIH “committed more than \$393 million” to support autoimmune disease research (ADCC, 2000). A congressional conference report<sup>38</sup> stated that NIAID was being appropriated more funding for FY 1999 than the House and Senate had requested, urged NIAID to expand autoimmune disease research, and pointed to the ADCC to provide greater coordination and focus for such research, which likely facilitated the ADCC’s charge.

The ADCC released reports in 2000, 2002, and 2005, each with a different focus and purpose. The ADCC’s initial report summarized the state of autoimmune disease research and funding at NIH and identified the major challenges facing autoimmune diseases research (ADCC, 2000):

1. “Development of a mechanism-based, conceptual understanding of autoimmune disease;
2. Translation of this knowledge into new, broadly applicable strategies for treatment and prevention of multiple diseases; and
3. Development of sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals.”

The subsequent ADCC report in 2002 (ADCC, 2002) was an autoimmune diseases research plan that had been requested by Congress, and it was informed by an expert panel that identified priority areas for autoimmune diseases research and considerations for implementing the research plan. The research plan had four major areas of emphasis:

- “reducing the burden of disease;
- enhancing understanding of disease etiology;

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<sup>37</sup> Personal communication. Ellen Goldmuntz, MD, PhD, Section Chief, Rheumatologic Autoimmune Disease Section, NAIID. August 11, 2021.

<sup>38</sup> *Omnibus Consolidated and Emergency Supplemental Appropriations Act, 1999*. Public Law 105-277, 105th Cong. (October 21, 1998). Conference Report 105-825 to accompany H.R. 4328.

- improving diagnosis, treatment, and prevention;
- increasing training, education; and
- information dissemination activities.”

The report underscored the importance of leveraging scientific and clinical knowledge to inform multiple autoimmune diseases and coordinating efforts to efficiently utilize available resources in both federal and private agencies, among others (ADCC, 2002). The report also called for Congress to appropriate additional funds in support of research in autoimmunity. Congress authorized funding for developing the ADCC research plan through amendments to the Children’s Health Act of 2000 (ADCC, 2002). A resolution submitted in the House in 2004<sup>39</sup> called for increase in appropriations to carry out the autoimmune diseases research. The committee, however, was unable to find additional information on appropriations for the research plan or its implementation.

The final ADCC report published in 2005 summarized progress made since the publication of the research plan in 2002 and pointed to funded and soon-to-be funded activities that signify NIH’s commitment to making progress in the areas identified in the research plan and encouraged continued investments in those areas. The ADCC reports ceased after the NIH Reform Act of 2006, which consolidated all the disparate reports required by law from NIH ICs in one comprehensive biennial report to Congress. As of FY 2016, NIH has further consolidated biennial reporting into a triennial report (ADCC, 2005).

The amount of NIH reporting to Congress on autoimmune diseases has changed over time. The ADCC reports ran 33 to 145 pages. In the NIH biennial reports for the years FY 2006 to 2009, the autoimmune disease section, which included type 1 diabetes, ran 14 to 19 pages, and in the reports for FY 2010 to 2013, including a new section on type 1 diabetes, autoimmune disease reporting ran 9 to 12 pages. For the FY 2014 to 2015 report, including a new diabetes section that intermixed type 1 and type 2 diabetes, autoimmune disease reporting ran 17 pages. In the most recent report, the first triennial report for the period FY 2016 to 2018, after including the section combining type 1 and type 2 diabetes, the content on autoimmune disease totaled 21 pages. The field of autoimmune disease research at NIH has expanded over time, yet the amount of reporting

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<sup>39</sup> Expressing the sense of the House of Representatives with respect to the level of funding provided to the National Institutes of Health for carrying out the Autoimmune Diseases Research Plan H.Res.610, 108th Cong. 2nd sess. (April 28, 2004).

to Congress on NIH activities and priorities in the field appears to have diminished.<sup>40</sup>

While the ADCC continues to be active to date, the committee was unable to identify information from publicly available sources to indicate the extent to which the ADCC's activities contribute to research and funding priorities at NIH. The agenda for the last ADCC public meeting held in May 2020 focused on celiac disease, a topic the group pursued after congressional language addressed concerns about the disease, and featured invited speakers who addressed research gaps and opportunities and unmet needs according to patients (ADCC, 2020). As a follow-up to this meeting, "NIH plans to develop a Research, Condition, and Disease Category (RCDC) report for celiac disease within the NIH Research Portfolio Online Reporting Tools (RePORT) website" (NIH, 2021c). Establishing a celiac disease RCDC category will make all NIH-funded projects related to celiac disease available in a publicly accessible format. In addition, in FY 2021, NIAID is "developing a Notice of Special Interest to encourage investigator-initiated celiac disease research." The ADCC is now using the process it used for celiac disease to explore other gaps and topics of interest to the community.<sup>41</sup> An earlier public meeting held in April 2019 introduced the Accelerating Medicines Partnerships (AMP), a collaborative initiative for autoimmune diseases sponsored by NIAMS, NIAID, and other non-NIH partners (ADCC, 2019). Currently, the IC representatives on the ADCC convene regularly to review shared priorities and activities, but information about these meetings is not available to the public, so the committee is unable to report on the scope of current ADCC activities.<sup>42</sup>

Since its establishment, the ADCC has played a role in coordinating research activities for autoimmune diseases across the ICs and with non-NIH external partners. Based on the review of available public information about the ADCC, and interviews with NIAID representatives, the committee notes that the ADCC functions as a convener of ICs and external partners and provides a forum for ICs to share information and coordinate their activities on autoimmune disease research. Outside of ADCC meetings, ICs may decide to develop or support collaborative research activities influenced in part by their participation in ADCC meetings, but this was difficult to assess from public documents. Currently, the ADCC

<sup>40</sup> The committee is aware that information on autoimmune diseases may appear in the biennial and triennial reports in sections other than the autoimmune disease and diabetes sections. The intention was to estimate the clearly indicated content on autoimmune disease in the reports.

<sup>41</sup> Personal communication. Ellen Goldmuntz, MD, PhD, Section Chief, Rheumatologic Autoimmune Disease Section, NIAID. August 11, 2021.

<sup>42</sup> Personal communication. Ellen Goldmuntz, MD, PhD, Section Chief, Rheumatologic Autoimmune Disease Section, NIAID. May 11, 2021.

has no dedicated funding or staff; NIH staff who support ADCC operations do so as part of their general work responsibilities.

### Other Modes of Coordination and Collaboration

The committee investigated other mechanisms by which NIH coordinates and collaborates on autoimmune disease research, both across NIH and external to NIH. For example, NIH established the Center for Human Immunology, Autoimmunity, and Inflammation as an NIH-wide “intramural initiative designed to study the human immune system” (NIH, 2012). Originally, its operation was supported jointly by several ICs, and this coordination and collaboration resulted in a study on human response to influenza vaccine that was collectively useful.<sup>43</sup> However, the Center could not sustain this funding model, partly because of difficulties in reaching agreement on projects that could yield benefit to all contributors, and eventually the Center was placed in NIAID.

NIH and FDA created the intramural NIH–FDA Immunology Interest Group in the 1990s as a part of an effort to foster interaction among scientists across both NIH and FDA, then located on the Bethesda campus.<sup>44</sup> It is one of the largest of such NIH groups and has led to offshoot groups. Speakers invited from within and outside NIH deliver weekly video seminars that anyone can view, and a large and active Listserv of some 1,500 listees further encourages collaboration. The Immunology Interest Group connects trainees and younger investigators with more established investigators across NIH and external experts, with a major vehicle being an annual workshop internal to NIH and FDA where approximately 400 attendees present abstracts and posters on active and unpublished work. The workshop, which the ICs jointly support, includes talks by intramural and extramural investigators who interact with trainees.

At the request of Congress, NIH established the NIAMS-led Lupus Federal Working Group (LFWG) in 2003 to facilitate collaboration on SLE “among NIH components, other federal agencies, voluntary and professional organizations, and industry groups with an interest in lupus” (NIAMS, 2019). With the help of LFWG and others, NIAMS published *The Future Directions of Lupus Research* in 2007, intended to guide the U.S. investment in SLE research (NIAMS, 2020a) and a follow-up *Action Plan*

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<sup>43</sup> Personal communication. Daniel Kastner, MD, PhD, Scientific Director, Division of Intramural Research Head, Inflammatory Disease Section, National Human Genome Research Institute, NIH, August 30, 2021.

<sup>44</sup> Personal communication. Pamela L. Schwartzberg, M.D., Ph.D, Chief, Cell Signaling and Immunity Section, NIAID; Senior Investigator, NHGRI, NIH, September 3, 2021.

for Lupus Research in 2015 (NIAMS, 2020a).<sup>45</sup> The latter was intended to “inform priority-setting processes among all lupus-related organizations” (NIAMS, 2015, 2020a) but not to dictate approaches to research or to compete with NIAMS’s strategic plans.<sup>46</sup> In addition to inviting experts to deliver talks, LFWG meetings serve as a forum for hearing patient concerns and disseminating information among members.

The National Institutes of Health Reform Act of 2006<sup>47</sup> directed NIH to establish DPCPSI, which sits within the NIH OD (DPCPSI, 2021). One of the Division’s responsibilities is to coordinate the research and activities of the various Offices that operate within the OD, such as the Office of AIDS Research and the Office of Research on Women’s Health (ORWH) (DPCPSI, 2021). The missions of these Offices vary, but in general they serve to enhance and promote the research of focus by coordinating and integrating activities across NIH’s intramural and extramural activities, as well as to stimulate and support research, disseminate research results, educate the public, and foster the development of a workforce for the field (OBSSR, 2021; ORWH, 2021b; SGMRO, 2021). Establishing an office requires having a research focus that cuts across most NIH ICs, with the office addressing concerns, particularly roadblocks, that the ICs share.<sup>48</sup> For example, NIH-funded researchers were inconsistent in the ways they recorded sex in clinical and animal trials, and while it was unlikely that a single IC would undertake advancing the policies and tools to capture these data in a uniform manner, it was appropriate for ORWH to do so. Similarly, ORWH initiated the Building Interdisciplinary Research Careers in Women’s Health program, a career development program, which “connects junior faculty to senior faculty with a shared interest in women’s health and sex differences research” (ORWH, 2021a). DPCPSI’s budget funds the activities of the NIH Offices and their staffs. Although the Offices can fund research, most can only do so by collaborating with one or more ICs. Each Office has a coordinating committee of IC representatives that serves as a primary coordinating hub to identify areas of need, gather consensus, and identify funding opportunities. The Offices release strategic plans, and the NIH triennial report to Congress describes Office activities.

<sup>45</sup> Available at <https://www.niams.nih.gov/about/working-groups/lupus-federal/action-plan> (accessed December 6, 2021).

<sup>46</sup> Personal communication. Marie Mancini, PhD, Program Director, Systemic Autoimmune Diseases Biology, Division of Extramural Research, NIAMS, NIH, September 7, 2021.

<sup>47</sup> PL 109-482.

<sup>48</sup> Personal communication. James M. Anderson, M.D., Ph.D., DPCPSI Director, September 7, 2021.

## Opportunities for IC Collaboration During the CSR Review Process

Independent of the efforts of the ADCC to coordinate autoimmune disease research activities, ICs can take steps among themselves to coordinate their research interests. The CSR review process, as noted earlier, presents an opportunity for ICs to collaborate on research activities, including collaborating on research funding for autoimmune diseases. CSR reviews all unsolicited grant applications and assigns them the appropriate IC for funding according to guidelines the ICs provide (Hodge, 2021). Those guidelines direct CSR on how to address grant applications that tackle areas of shared interest for multiple ICs. ICs may also “bid” to be part of grants that they have an interest in, which offers an opportunity for ICs to collaborate on studies that can leverage their mutual expertise and resources.<sup>49</sup> Since the committee did not have further access to materials governing this process or additional details on the process, it is unclear how well this process works and the frequency with which ICs bid on and collaborate on projects.

## Major NIH Initiatives Involving Collaboration

A number of recent and ongoing initiatives provide evidence of collaboration on autoimmune disease research across ICs as well as including other federal agencies and external organizations and researchers. Institute representatives, during their meetings with the committee, along with information on IC websites, highlighted the major initiatives below.

### *Collaborations Among ICs*

**Clinical Islet Transplant (CIT) Consortium.**<sup>50</sup> *Type 1 diabetes* (CIT Consortium, 2021).

- Collaborators include:
  - NIDDK
  - NIAID
  - Principal investigators and research centers in the United States and Sweden
- Description: “The CIT Consortium is a network of clinical centers and a data coordinating center established in 2004 to conduct

<sup>49</sup> According to multiple NIH speakers who spoke at the committee’s public information-gathering sessions (Goldmuntz, 2020; Hodge, 2021; McNamara, 2021).

<sup>50</sup> Website available at <https://www.citisletstudy.org/what.html> (accessed December 2, 2021).

studies of islet transplantation in patients with type 1 diabetes. Studies conducted by the CIT Consortium focus on improving the safety and long-term success of methods for transplanting islets, the insulin-producing cells of the pancreas, in people whose own islets have been destroyed by the autoimmune process that characterizes type 1 diabetes.”

Principal areas of focus include:

- “improving the isolation and viability of islets
- reducing complications of the islet transplant procedure, (e.g., bleeding and clotting in the blood vessels of the liver)
- reducing the side effects of immunosuppression
- achieving good blood sugar control without hypoglycemia
- following the fate of islets after transplantation and determining why donor islets sometimes fail
- evaluating new ways to safely prevent immune rejection of donor tissues.”

#### **Autoantigens and Neoantigens Function in the Etiology and Pathophysiology of Type 1 Diabetes.** *Type 1 diabetes* (NIH et al., 2021d).

- Collaborators include:
  - NIDDK
  - NIAID
- Description: The purpose of this initiative is to characterize the “function of neoepitopes and neoantigens in type 1 diabetes. This includes the function that post-translational modifications might have in the humoral and cell mediated autoimmune responses and overall in the etiology and pathophysiology of type 1 diabetes.”

**Autoimmune Centers of Excellence (ACEs).**<sup>51,52</sup> *SLE, type 1 diabetes, inflammatory bowel disease, multiple sclerosis, pemphigus vulgaris, psoriasis, scleroderma, rheumatoid arthritis, and Sjögren’s disease* (ACE, 2020).

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<sup>51</sup> Website available at <https://www.autoimmunitycenters.org/mission.php> (accessed December 2, 2021).

<sup>52</sup> *Autoimmunity Centers of Excellence Progress Report 2021* is available at <https://www.autoimmunitycenters.org/ACE%20Public%20Progress%20Report%20Jan-31-2022%20DAIT.pdf> (accessed March 3, 2022).

- Collaborators include:
  - NIAID
  - NIDDK
  - NIH ORWH
  - Clinical research sites and principal investigators
- Description: “ACEs conduct collaborative basic and clinical research on autoimmune diseases. Close interaction between clinicians and basic researchers accelerates the discovery, development, and translation of therapies for autoimmune diseases from the lab to use in the clinic.” The principal areas of focus include:
  - Encouraging and enabling collaborative research—“across scientific disciplines, across medical specialties, and between basic and clinical scientists—in the search for effective treatments for autoimmune diseases”
  - Evaluating the safety and efficacy of treatment strategies for autoimmune diseases
  - Exploring the immune mechanisms underlying the agents evaluated in these ACE clinical trials.

**Office of Rare Diseases Research.**<sup>53</sup> A rare disease is defined as “a condition that affects fewer than 200,000 people in the United States,” which includes some autoimmune diseases (NCATS, 2021b).

- Collaborators include:
  - The Office sits in NCATS but is NIH-wide (NCATS, 2021a)
- Description: This Office facilitates and coordinates NIH-wide activities that involve research for a broad range of rare diseases, including autoimmune diseases. Duties of the Office include:
  - Developing and maintaining a centralized database on rare diseases.
  - Coordinating and providing liaison with organizations worldwide concerned with rare diseases research and orphan products development.
  - Advising the Office of the Director on matters related to NIH-sponsored research involving rare diseases.
  - Responding to information and policy requests about rare diseases.

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<sup>53</sup> Website available at <https://ncats.nih.gov/about/center/org/ordr> (accessed December 2, 2021).

*Collaborations Among ICs and External Agencies, Organizations, and Industry*

**Myasthenia Gravis Rare Disease Network (MGNet).**<sup>54</sup> *Myasthenia gravis and its subtypes* (Rare Diseases Clinical Research Network, 2021).

- Collaborators include:
  - NCATS
  - NINDS
  - Myasthenia Gravis Foundation of America
  - Industry (not named)
  - Academic medical centers
- Description: The “Myasthenia Gravis Rare Disease Network serves as a centralized, international consortium for physicians, scientists, patient advocacy groups, as well as industry partners to develop resources and implement ideas to enhance discovery, treatment, and advocacy for the patient community. The immediate goals of MGNet are to further define how patients respond to conventional treatments over time, evaluate a novel drug for therapy of some forms of MG, find biological markers of the disease (biomarkers), and encourage new scientists to engage in research on MG.”

**Accelerating Medicines Partnership® (AMP®) Program including Autoimmune and Immune-Mediated Diseases (AMP® AIM).**<sup>55</sup> *Rheumatoid arthritis, SLE, psoriatic spectrum diseases, and Sjögren’s disease* (NIAMS, 2021a; NIH, 2021b).

- Collaborators include:
  - NIAMS
  - NIAID
  - NIDCR (NIH et al., 2021a)
  - ORWH
  - FDA (NIH, 2021b)
  - European Medicines Agency
  - Multiple biopharmaceutical and life science companies
  - Multiple nonprofit organizations
- Description: The purpose of the AMP® and AMP® AIM program is to establish disease teams that will focus on autoimmune and immune-mediated diseases, including rheumatoid arthritis,

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<sup>54</sup> Website available at <https://www.rarediseasesnetwork.org/mgnet> (accessed December 2, 2021).

<sup>55</sup> The AMP® AIM program expands and builds upon the AMP® RA/SLE program.

SLE, psoriatic spectrum diseases, and Sjögren's disease, with the goal of developing a thorough understanding of the cellular and molecular disease pathways and identifying novel targets for intervention.

**Immune Tolerance Network (ITN).**<sup>56</sup> *Type 1 diabetes, SLE, multiple sclerosis* (Immune Tolerance Network, 2021).

- Collaborators include:
  - NIAID
  - NIDDK
  - The Juvenile Diabetes Research Foundation
  - Clinical sites and investigators worldwide
- Description: ITN's purpose is "to advance the clinical application of immune tolerance by performing high-quality clinical trials of emerging therapeutics integrated with mechanism-based research. In particular, [they] aim to establish new tolerance therapeutics, develop a better understanding of the mechanisms of immune function and disease pathogenesis, [and] identify new biomarkers of tolerance and disease." ITN conducts research on organ and cellular transplantation, autoimmune diseases, allergy, asthma, and type 1 diabetes. ITN collaborates with academic, government, and industry leaders to develop and fund cutting-edge immune tolerance research.

**Environmental Determinants of Diabetes in the Young (TEDDY) Study.**<sup>57</sup> *Type 1 diabetes* (TEDDY Study Group, 2008).

- Collaborators include:
  - NIDDK
  - NIAID
  - NICHD
  - NIEHS
  - CDC
  - Juvenile Diabetes Research Foundation
  - Clinical centers in the United States and Germany, Sweden, and Finland
- Description: The long-term goal of the TEDDY study—an observational study that enrolled 8,668 participants with a 2025 estimated completion date—"is the identification of infectious

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<sup>56</sup> Website available at <https://www.immunetolerance.org> (accessed December 2, 2021).

<sup>57</sup> Website available at <https://teddy.epi.usf.edu> (accessed December 2, 2021).

agents, dietary factors, or other environmental agents, including psychosocial factors which trigger [type 1 diabetes] in genetically susceptible individuals or which protect against the disease. Identification of such factors will lead to a better understanding of disease pathogenesis and result in new strategies to prevent, delay, or reverse [type 1 diabetes]." (Clinicaltrials.gov, 2021).

**Type 1 Diabetes Trial Net (TrialNet).**<sup>58</sup> *Type 1 diabetes* (TrialNet, 2018).

- Collaborators include:
  - NIDDK
  - NIAID (ADCC, 2005)
  - NICHD (NIH et al., 2021e)
  - National Center for Complementary and Alternative Medicine (NIH, 2021e)
  - Juvenile Diabetes Research Foundation (TrialNet, 2018)
  - American Diabetes Association
  - Helmsley Charitable Trust
  - International network of researchers
- Description: TrialNet is an international network of researchers exploring ways to prevent, delay, and reverse the progression of type 1 diabetes (TrialNet, 2018). TrialNet was established in response to the Surgeon General's Report *Healthy People 2000*, which identified diabetes as a national health objective for the nation. In response to the report, Congress created the Diabetes Research Working Group to develop a plan for diabetes research. One of the group's recommendations was to conduct additional research studies and clinical trials on type 1 diabetes prevention.

## SUMMARY

NIH is the primary funding agency for biomedical research, including autoimmune disease research. In 2020, NIH spent more than \$1 billion on autoimmune disease research. Currently, 12 of 24 ICs provide the majority of funding to support extramural investigator-initiated autoimmune disease research, and 11 of 24 ICs provide funding to support intramural autoimmune disease research programs. Each IC has a different mission, and often has different research priorities and focuses on different autoimmune diseases than the other ICs. The autoimmune disease research focus of each IC ranges across basic, translational, and clinical research, and sometimes ICs have overlapping missions in autoimmune disease

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<sup>58</sup> Website available at <https://www.trialnet.org> (accessed December 2, 2021).

research. These overlapping missions could impede the coordination of autoimmune disease research programs.

The committee identified evidence of attempts to coordinate funding and research efforts, but it was difficult for the committee to assess the effectiveness of these efforts. While the ADCC continues to be active to date, the committee was unable to determine the extent to which the ADCC's activities contribute to setting research and funding priorities for autoimmune disease research at NIH. The lack of standardization of the process of strategic planning across ICs and consistency in the release of strategic plans by individual ICs has important implications, since it may pose an obstacle for ICs in coordinating their strategic planning efforts, and subsequently, their funding and research efforts for autoimmune diseases.

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## Analysis of Institute and Center Autoimmune Disease Research Activity

Both extramural and intramural autoimmune disease research occurs across the various Institutes, Centers, and Offices at the National Institutes of Health (NIH), including the Office of the Director (OD). As noted in Chapter 5, total spending for autoimmune disease research was \$1,083,000,000 for fiscal year (FY) 2020 (NIH, 2020a), a 2.6 percent increase from FY 2019. NIH's investment in autoimmune disease research has remained constant at about 2.8 percent of its total obligations between 2008 and 2020 (Figure 6-1).<sup>1,2</sup>

From 2015 to 2020, total NIH obligations increased by 40 percent, whereas autoimmune disease spending increased by approximately 34 percent. Over the 2008–2020 period, NIH-funded autoimmune disease research activities totaled approximately \$11.7 billion. The highest levels of spending on autoimmune disease occurred in 2009 and more recently in 2020 (Figure 6-2).

As noted in Chapter 5, some Institutes and Centers (ICs) have a greater focus on autoimmune diseases tied to their mission, and thus there is considerable variation in the level of spending on autoimmune disease research activities. The OD also contributes funds to support autoimmune disease research activities. Table 6-1<sup>3</sup> shows total Institute, Center, and OD obligations, autoimmune disease spending, autoimmune

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<sup>1</sup> All NIH RePORTER data used in this report was accessed on July 16, 2021.

<sup>2</sup> See Appendix G for methodology.

<sup>3</sup> See Appendix G for methodology.

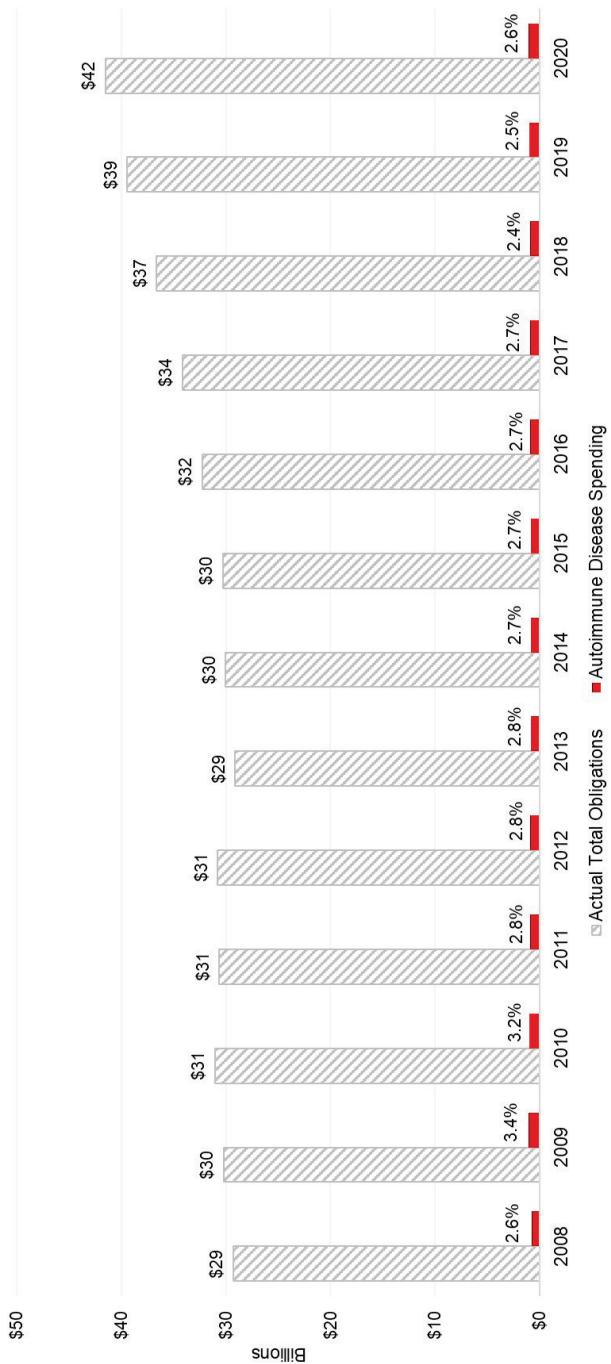
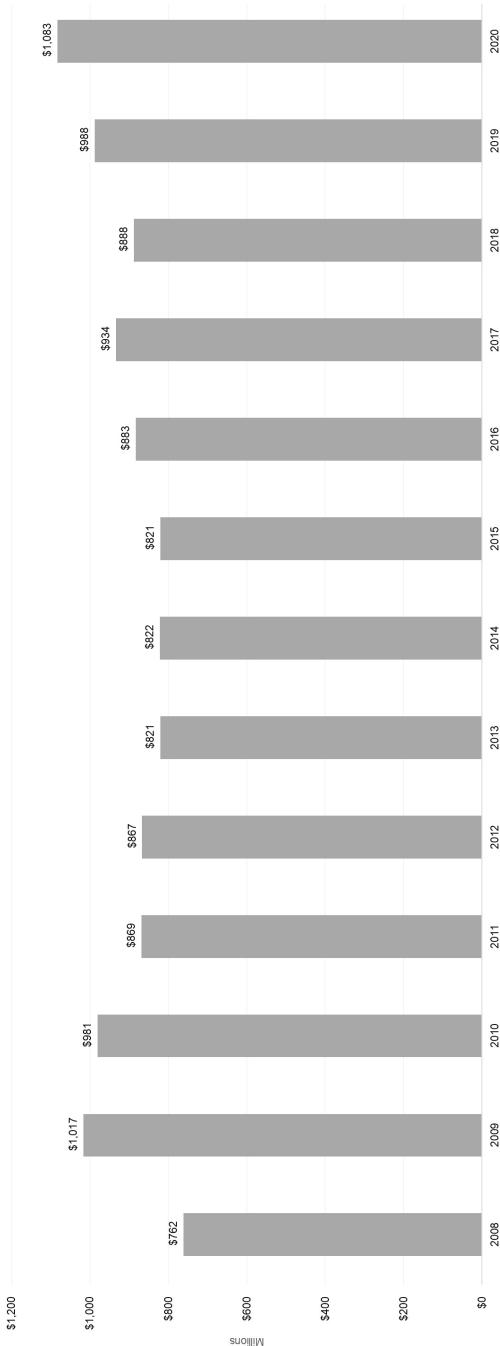


FIGURE 6-1 NIH actual total obligations and autoimmune disease spending, FY 2008–2020.

SOURCES: NIH, 2020a, 2021b.



**FIGURE 6-2** NIH autoimmune disease spending, FY 2008–2020.

NOTE: FY, fiscal year.

SOURCE: NIH, 2020a.

**TABLE 6-1** IC FY 2020 Actual Total Obligations, Autoimmune Disease Spending, and Average Autoimmune Disease Spending for FY 2008–2020

IC	FY 2020 Actual Total Obligations	FY 2020 Autoimmune Disease Spending	FY 2020 Percent Au- toimmune Spending	Average Autoimmune Disease Spending, FY 2008–2020
NCI	\$6,418,988,000	\$35,369,000	0.5	\$24,973,000
NIAID	\$5,880,084,000	\$278,303,000	4.7	\$209,707,000
NHLBI	\$3,624,863,000	\$76,372,000	2.1	\$65,729,000
NIGMS	\$2,937,142,000	\$15,653,000	0.5	\$13,682,000
NINDS	\$2,443,099,000	\$79,386,000	2.2	\$75,439,000
NIDDK	\$2,220,977,000	\$347,207,000	15.6	\$282,810,000
NICHD	\$1,556,841,000	\$10,516,000	0.7	\$15,975,000
NIEHS	\$883,808,000	\$12,023,000	1.4	\$13,619,600
NCATS	\$832,856,000	\$8,757,000	1.0	\$3,259,000
NEI	\$823,310,000	\$33,983,000	4.1	\$26,219,000
NIAMS	\$624,832,000	\$147,716,000	23.6	\$130,857,000
NHGRI	\$604,083,000	\$10,469,000	1.7	\$10,434,000
NIDCR	\$477,644,000	\$18,880,000	3.9	\$16,727,000
OD	\$1,467,130,000	\$14,910,000	3.1	\$21,649,000

NOTES: ICs are arranged in descending order according to FY 2020 actual total obligations. The Office of the Director (OD) is not an institute but is included because of its funding contributions to autoimmune disease research. FY, fiscal year; IC, Institute or Center; NCATS, National Center for Advancing Translational Sciences; NCI, National Cancer Institute; NEI, National Eye Institute; NHGRI, National Human Genome Research Institute; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIDCR, National Institute of Dental and Craniofacial Research; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS, National Institute of Environmental Health Sciences; NIGMS, National Institute of General Medical Sciences; NINDS, National Institute of Neurological Disorders and Stroke; OD, Office of the Director.

SOURCES: NIH, 2021b, 2021f.

spending as a percentage of total obligations, and average spending over the 2008–2020 period.

In 2020, the ICs with the highest level of spending on autoimmune disease research were the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). NIAMS autoimmune disease spending as a percentage of actual total obligations was the highest at 23.6 percent, followed by NIDDK (15.6 percent). Although NIAID had the third highest level of autoimmune disease spending, it was only about 5 percent of its total obligations in FY 2020. These three Institutes also had the highest average spending on autoimmune disease research during the 2008–2020 period. In 2020, of the total \$1,125,730,564 spent on autoimmune disease research, NIDDK (30.8 percent), NIAID (24.7 percent) and NIAMS (13.1) spending accounted for almost 70 percent of the total autoimmune disease spending (Table 6-2).<sup>4</sup>

## CHARACTERISTICS OF RESEARCH ACTIVITIES SUPPORTED BY ICS

NIH uses 245 activity codes to characterize the funding mechanisms it employs to fund diverse activities. The committee focused on a select number of activity codes to characterize NIH- and IC-funded autoimmune disease research activities. The committee used RePORTER activity code data to assess autoimmune disease research activities by extramural research (R and P grants); cooperative agreements (U grants); and fellowship, training, and training center activities (F, K, and T grants); and intramural research activities (Z grants) (Table 6-3). Figure 6-3 provides NIH autoimmune disease funding for R, U, and P grants for FY 2008–2020 and the average funding for these grants over that period.

Research project (R) grant funding for autoimmune disease research was highest in 2020 and lowest in 2008 and during 2013–2016. Funding for cooperative agreements (U) grants was greater than funding for research program project and center grants (P) during FY 2008–2020. Funding for cooperative agreements increased from 2008 to 2017, dropped in 2018, and began to rise again in 2019 and 2020. Funding for research programs project and centers was slightly higher in 2009–2011 and remained constant after 2011.

Training grants contribute to building the autoimmune disease research workforce and to advancing research. Table 6-4<sup>5</sup> shows NIH funding for fellowships (F), research career programs (K), and institutional

<sup>4</sup> See Appendix G for methodology.

<sup>5</sup> See Appendix G for methodology.

**TABLE 6-2** IC FY 2020 Autoimmune Disease Spending and Percentage of Total NIH 2020 Autoimmune Disease Spending

IC	FY 2020	Percent of Total
NCI	\$35,369,000	3.1%
NIAID	\$278,303,000	24.7%
NHLBI	\$76,372,000	6.8%
NIGMS	\$15,653,000	1.4%
NINDS	\$79,386,000	7.1%
NIDDK	\$347,207,000	30.8%
NICHD	\$10,516,000	0.9%
NIEHS	\$12,023,000	1.1%
NCATS	\$8,757,000	0.8%
NEI	\$33,983,000	3.0%
NIAMS	\$147,716,000	13.1%
NHGRI	\$10,469,000	0.9%
NIDCR	\$18,880,000	1.7%
OD	\$14,910,000	1.3%
All Other ICs	\$36,186,000	3.2%
<b>Total</b>	<b>\$1,125,731,000</b>	<b>100.0%</b>

NOTES: ICs are arranged in descending order according to FY 2020 actual total obligations. The Office of the Director (OD) is not an institute but is included because of its funding contributions to autoimmune disease research. FY, fiscal year; IC, Institute or Center; NCATS, National Center for Advancing Translational Sciences; NCI, National Cancer Institute; NEI, National Eye Institute; NHGRI, National Human Genome Research Institute; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIDCR, National Institute of Dental and Craniofacial Research; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS, National Institute of Environmental Health Sciences; NIGMS, National Institute of General Medical Sciences; NINDS, National Institute of Neurological Disorders and Stroke; OD, Office of the Director.

SOURCE: NIH, 2021f.

**TABLE 6-3** Committee-Reviewed NIH Grant Types, by Activity Code

NIH Grant Types		
Activity Code		Purpose
<b>Extramural Research</b>		
R	Research Projects	Research project grants may be awarded for discreet, specific research projects to individuals at universities, medical and other health professional schools, colleges, hospitals, research institutes, for-profit organizations, and government institutions. Typically, these grants are awarded for 3 to 5 years. The most common R award is the R01.
P	Research Program Projects and Centers	Program project / center grants are large, multidisciplinary, and long-term research efforts that generally include a diverse array of research activities.
<b>Cooperative Agreements</b>		
U	Cooperative Agreements	Cooperative agreements are a support mechanism frequently used for complex, high-priority research areas that require substantial involvement from NIH program or scientific staff.
<b>Fellowships, Training, Training Centers</b>		
F	Fellowship Programs	Fellowships provide individual research training opportunities (including international) for trainees at the undergraduate, graduate, and postdoctoral levels.
K	Research Career Development Programs	Research Career Development awards provide individual and institutional research training opportunities (including international) to trainees at the undergraduate, graduate, and postdoctoral levels.

**TABLE 6-3** Continued

T	Institutional Training Programs	Institutional Training awards enable institutions to provide individual research training opportunities (including international) for trainees at the undergraduate, graduate, and postdoctoral levels.
<b>Intramural Research</b>		
Z	Intramural research	Z grants support research activities of NIH intramural researchers.

SOURCES: NIH, 2019; NIH Grants & Funding, 2021.

training programs (T). Research career program grants had higher levels of funding throughout the entire period.

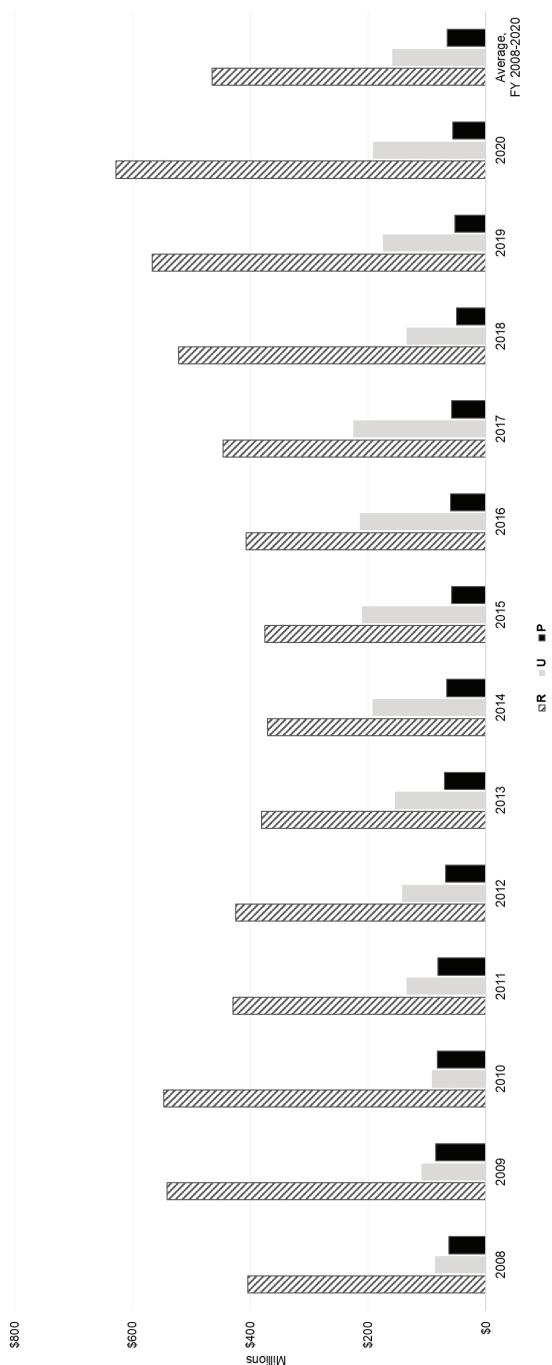
The committee examined the proportion of autoimmune disease spending used for training to total autoimmune disease spending and compared it to other Research, Condition, and Disease Categories (RCDC) spending categories (Table 6-5). The comparison groups are chronic diseases and are more common in women or have a similar prevalence between men and women (cardiovascular).

## IC FUNDING OF GRANTS

To explore ICs' use of grants to further autoimmune disease research, the committee examined IC funding for research (R), cooperative agreement (U), program project/center (P) and training (F, K, T) grants. Figure 6-4 and Figure 6-5 present funding of R grants categorized by ICs with the largest research budgets and smaller research budgets.

For the purposes of this report, ICs are arranged in order by budget level and have been separated into two categories: large ICs and small ICs. Large ICs have FY 2020 actual total obligations greater than \$1 billion, and small ICs have actual total obligations of less than \$1 billion. Among the larger ICs, NIDDK and NIAID had the highest level of funding for R grants in FY 2020. NIDDK had the highest level of average autoimmune disease research funding compared with the other ICs. Among the smaller ICs, NIAMS had a significantly higher level of funding in 2020 and average of funding for 2008–2020 for R grants to support autoimmune disease research compared to other small ICs. The OD spent an average of \$10 million on autoimmune disease research grants, which was comparable to the average funding spent by other smaller ICs.

U grants support research activities that NIH considers to be complex and of high-priority research areas. Unlike independent investigator R grants, U grants require greater involvement from NIH program or



**FIGURE 6-3** NIH autoimmune disease funding by research (R), cooperative agreement (U), and research program project and center (P) grants, FY 2008–2020 (in millions).

NOTE: FY, fiscal year.  
SOURCE: NIH, 2021f.

**TABLE 6-4** Autoimmune Disease Spending: Fellowship, Research Career, and Training Program Grant Funding per FY 2008–2020 and Average over the Period

FY	Fellowship	Research Career	Training Program
2008	\$2,877,000	\$26,431,000	\$5,121,000
2009	\$3,636,000	\$28,202,000	\$4,778,000
2010	\$4,216,000	\$26,562,000	\$5,242,000
2011	\$3,880,000	\$27,727,000	\$4,981,000
2012	\$3,383,000	\$28,948,000	\$4,357,000
2013	\$3,634,000	\$29,209,000	\$4,749,000
2014	\$3,839,000	\$28,621,000	\$4,911,000
2015	\$3,935,000	\$27,736,000	\$4,388,000
2016	\$4,215,000	\$28,814,000	\$5,353,000
2017	\$4,130,000	\$28,133,000	\$5,756,000
2018	\$4,504,000	\$27,625,000	\$5,502,000
2019	\$4,582,000	\$29,746,000	\$5,025,000
2020	\$5,288,000	\$33,571,000	\$4,786,000
Average FY 2008–2020	\$4,009,000	\$28,564,000	\$4,996,000

NOTE: NIH autoimmune disease activity codes for fellowship (F), research career (K), and training program (T) grants. FY, fiscal year.

SOURCE: NIH, 2021f.

**TABLE 6-5** Training Investment for Selected RCDC Spending Categories, FY 2020

RCDC Spending Category	Fellowship	Research Career	Training	FY 2020 Total
Alzheimer's	10.9%	72.5%	16.5%	\$47,440,000
Autoimmune Disease	12.1%	76.9%	11.0%	\$43,646,000
Breast Cancer	0.8%	2.2%	0.0%	\$717,665,000
Cardiovascular	9.4%	64.3%	26.3%	\$144,080,000
COPD	12.2%	87.8%	0.0%	\$7,531,000

NOTE: COPD, chronic obstructive pulmonary disease; FY, fiscal year; RCDC, Research, Condition, and Disease Categorization.

SOURCE: NIH, 2021f.

scientific staff. Figures 6-6 and 6-7 show the level of funding for autoimmune disease U grants for large and small ICs.

Among the larger ICs (Figure 6-6), NIDDK had a significantly higher level of funding for U grants for autoimmune disease research activities in FY 2020 and over the FY 2008–2020 period. NIDDK funding levels for U grants over the period and in FY 2020 were more than double that of NIAID, the IC with the next level of U grant funding. Other large Institute funding of U grants was less than \$6 million in 2020. In FY 2020, NIAMS, among the smaller ICs (Figure 6-7) had the highest level of funding for U grants (\$9 million). During the FY 2008–2020 period, NHGRI had the highest average U grant funding level (\$7 million).

P grants support large, multidisciplinary, and long-term research on autoimmune disease. Figure 6-8 shows P grant funding levels of at least \$1 million by IC. NIAID and NIAMS had the highest funding levels for P grants and were similar, although NIAID has a larger overall research budget than NIAMS.

ICs can play an important role in supporting the research workforce in their area of focus. Funding can help build the research workforce through fellowships (F), research career programs (K), and institutional training programs (T) grants, in addition to traditional research grants. Table 6-6 shows IC funding of training grants that support the autoimmune disease research workforce. In FY 2020, NIDDK, NIAID, and NHLBI had the highest level of funding for F grants (\$2.0 million, \$814,000, and \$804,000 respectively). NIDDK also had the highest average funding of F grants over the FY 2008–2020 period (\$1.6 million).

Funding for K grants was higher than funding for F or T grants. In FY 2020, NIDDK had the highest level of funding of K grants (\$11.3 million), followed by NIAMS (\$8.2 million). Over the FY 2008–2020 period, NIDDK (\$9.8 million) and NIAMS (\$7.9 million) had the highest level of average funding for K grants compared to other ICs. The committee notes that OD funding for K grants was \$1.1 million in FY 2020, which is more than double than the average funding over the FY 2008–2020 period.

ICs other than NIAMS relied less on the T grant mechanism to support training of autoimmune disease researchers. In FY 2020, NIAMS funded \$3.9 million in T grants with an average funding level of \$4.2 million over the FY 2008–2020 period. NIAID, NIDDK, and OD used this mechanism at a significantly lower funding level.

**TABLE 6-6** Training Grant Funding for Autoimmune Disease Research by IC and FY

IC	Year(s)	F	K	T	Training as a Percent of FY 2020 Obligations
NCI	FY 2020	\$171,195	\$584,384	\$0	0.01%
	Average FY 2008–2020	\$100,885	\$349,586	\$0	
NIAID	FY 2020	\$814,263	\$2,085,385	\$653,017	0.06%
	Average FY 2008–2020	\$492,310	\$2,454,588	\$561,823	
NHLBI	FY 2020	\$804,583	\$4,432,189	\$0	0.14%
	Average FY 2008–2020	\$442,446	\$2,737,751	\$0	
NIGMS	FY 2020	\$79,212	\$198,504	\$0	0.01%
	Average FY 2008–2020	\$135,591	\$118,849	\$0	
NINDS	FY 2020	\$432,647	\$3,359,470	\$0	0.16%
	Average FY 2008–2020	\$586,329	\$2,324,825	\$0	
NIDDK	FY 2020	\$2,062,032	\$11,311,126	\$93,836	0.61%
	Average FY 2008–2020	\$1,640,982	\$9,848,175	\$159,663	
NICHD	FY 2020	\$82,851	\$570,283	\$0	0.04%
	Average FY 2008–2020	\$26,922	\$553,745	\$0	
NIEHS	FY 2020	\$36,611	\$87,463	\$0	0.01%
	Average FY 2008–2020	\$67,663	\$65,037	\$0	
NCATS	FY 2020	\$0	\$0	\$0	-
	Average FY 2008–2020	\$0	\$0	\$0	
NEI	FY 2020	\$0	\$916,394	\$0	0.11%
	Average FY 2008–2020	\$14,717	\$828,068	\$0	
NIAMS	FY 2020	\$281,015	\$8,247,061	\$3,953,872	2.00%
	Average FY 2008–2020	\$229,852	\$7,926,922	\$4,261,852	
NHGRI	FY 2020	\$64,926	\$0	\$0	0.01%
	Average FY 2008–2020	\$4,994	\$62,014	\$0	
NIDCR	FY 2020	\$107,672	\$0	\$0	0.02%
	Average FY 2008–2020	\$65,626	\$139,637	\$0	
OD	FY 2020	\$0	\$1,175,676	\$85,655	0.09%
	Average FY 2008–2020	\$9,502	\$491,711	\$12,694	

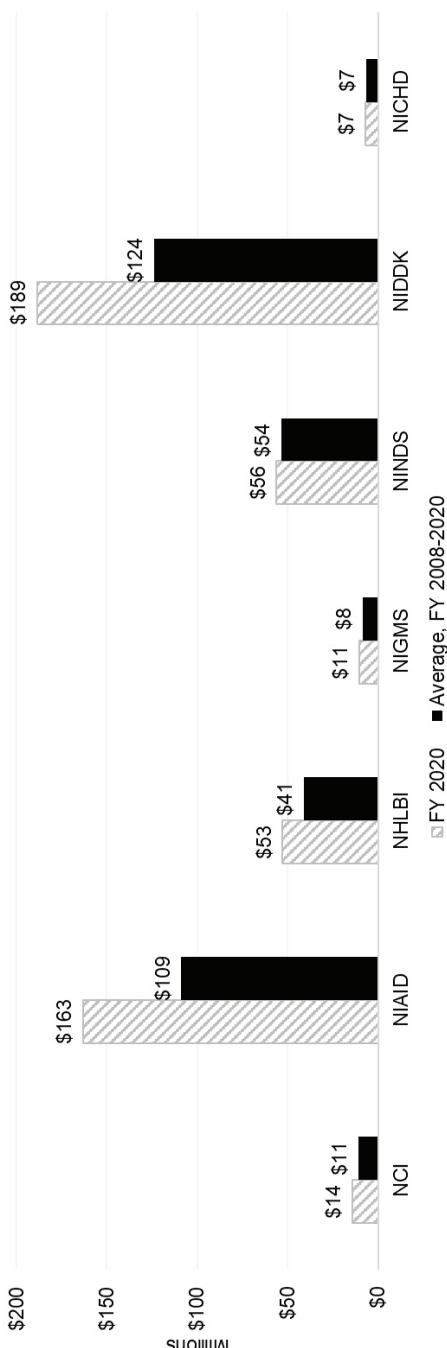
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**TABLE 6-6** Continued

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NOTE: FY, fiscal year; IC, Institute or Center; NCATS, National Center for Advancing Translational Sciences; NCI, National Cancer Institute; NEI, National Eye Institute; NHGRI, National Human Genome Research Institute; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIDCR, National Institute of Dental and Craniofacial Research; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS, National Institute of Environmental Health Sciences; NIGMS, National Institute of General Medical Sciences; NINDS, National Institute of Neurological Disorders and Stroke; OD, Office of the Director.

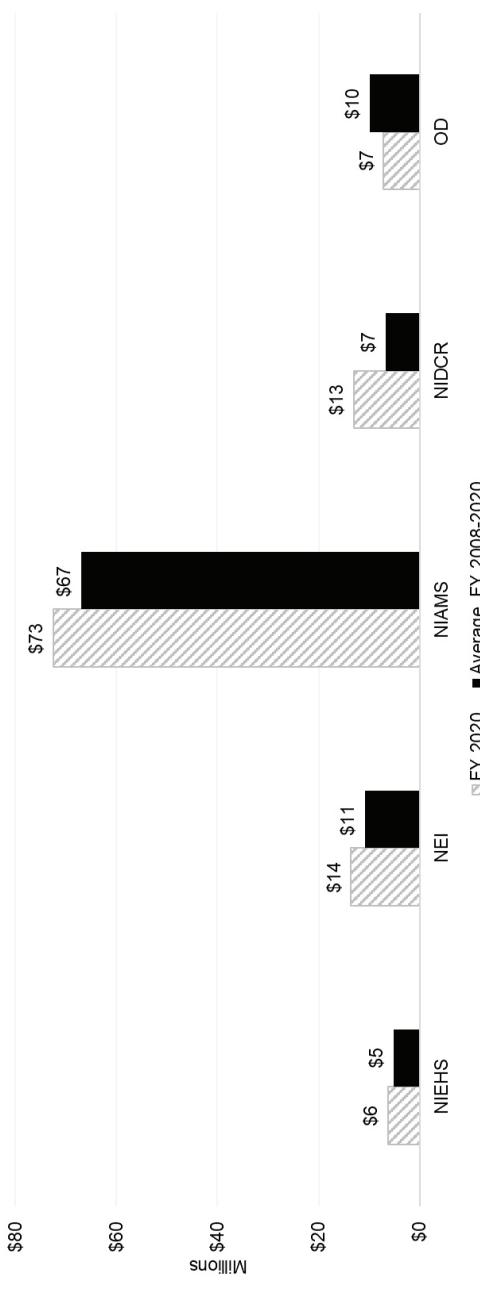
SOURCE: NIH, 2021f.



**FIGURE 6-4** IC funding for research (R) grants by large ICs for FY 2020 and average FY 2008–2020 (in millions).

NOTES: Large Institutes have FY 2020 actual total obligations greater than \$1 billion. FY, fiscal year; IC, Institute or Center; NIAID, National Institute of Allergy and Infectious Diseases; NCI, National Cancer Institute; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIGMS, National Institute of General Medical Sciences; NHLBI, National Heart, Lung, and Blood Institute; NINDS, National Institute of Neurological Disorders and Stroke.

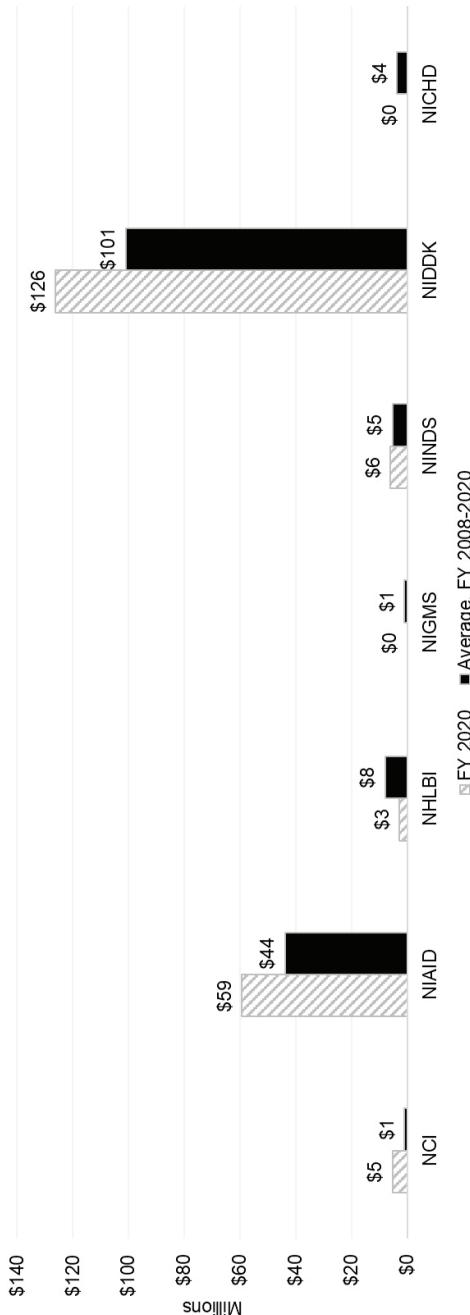
SOURCE: NIH, 2021f.



**FIGURE 6-5** IC funding for research (R) grants by small ICs for FY 2020 and average FY 2008–2020 (in millions).

NOTES: Small Institutes have FY 2020 actual total obligations less than \$1 billion. While the Office of the Director (OD) is not an institute, it is included in the small Institute category. National Human Genome Research Institute (NHGRI) did not fund R grants in 2020 but contributed an average of \$704,274 per year over the 2008–2020 period for autoimmune disease research. National Center for Advancing Translational Sciences (NCATS) was not included in the figure because it became an Institute in 2012; In FY 2020, NCATS spent \$226,174 on autoimmune disease research grants and an average of \$493,918 per year over the FY 2008–2020 period. FY, fiscal year; IC, Institute or Center; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIEHS, National Institute of Environmental Health Sciences; NEI, National Eye Institute; NIDCR, National Institute of Dental and Craniofacial Research.

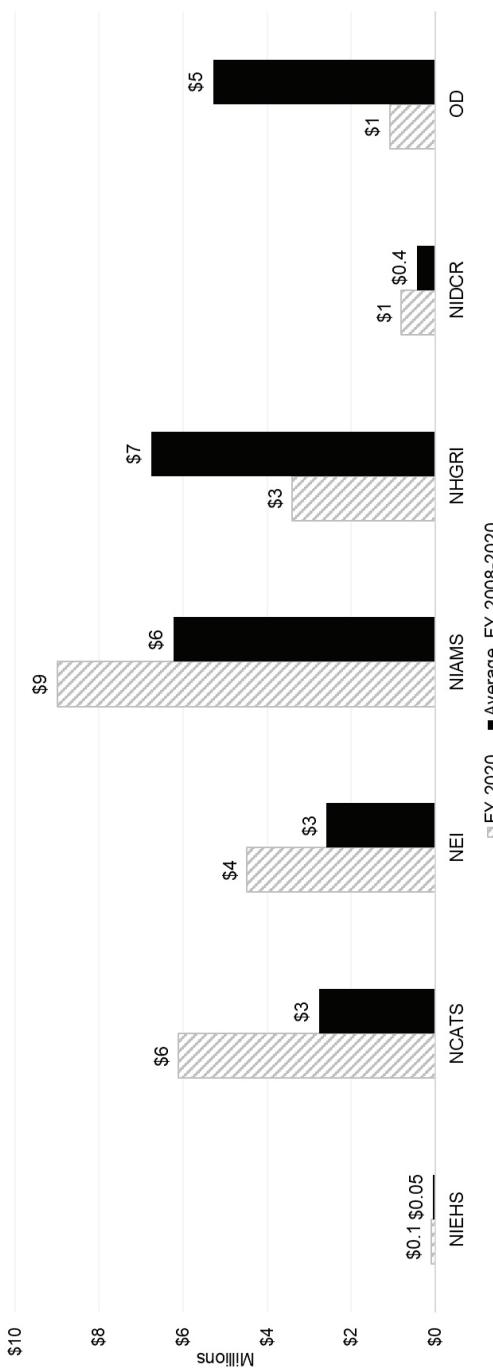
SOURCE: NIH, 2021f.



**FIGURE 6-6** IC autoimmune disease funding for cooperative agreement (U) grants for large ICs, FY 2020 and average FY 2008–2020 (in millions).

NOTES: Large Institutes have FY 2020 actual total obligations greater than \$1 billion. FY, fiscal year; IC, Institute or Center; NIAID, National Institute of Allergy and Infectious Diseases; NCI, National Cancer Institute; NICHD, *Emilie Kennedy Shriver* National Institute of Child Health and Human Development; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIGMS, National Institute of General Medical Sciences; NHLBI, National Heart, Lung, and Blood Institute; NINDS, National Institute of Neurological Disorders and Stroke.

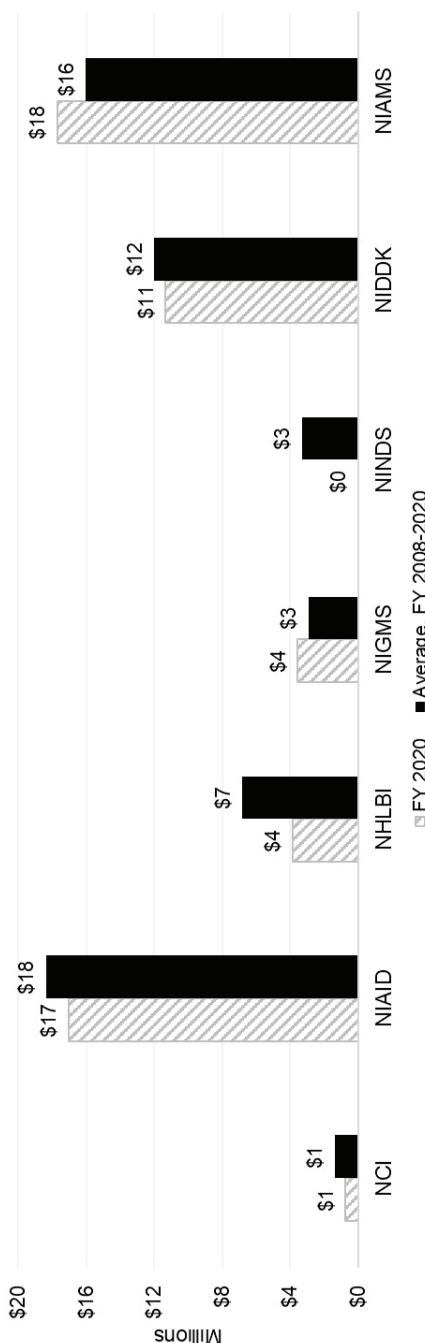
SOURCE: NIH, 2021f.



**FIGURE 6-7** IC autoimmune disease funding for cooperative agreement (U) grants for small ICs, FY 2020 and average FY 2008–2020 (in millions).

NOTES: Small Institutes have FY 2020 actual total obligations less than \$1 billion. While the Office of the Director (OD) is not an institute, it is included in the small Institute category. FY, fiscal year; IC, Institute or Center; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIEHS, National Institute of Environmental Health Sciences; NEI, National Eye Institute; NIDCR, National Institute of Dental and Craniofacial Research.

SOURCE: NIH, 2021f.



**FIGURE 6-8** IC autoimmune disease funding for program project/center (P) grants by ICs, FY 2020 and average FY 2008–2020 (in millions).

NOTES: Institutes with program / center (P) grant spending of less than \$1 million in 2020 or over the 2008–2020 period are not shown in the graph, including National Eye Institute (NEI), National Institute of Environmental Health Sciences (NIEHS), *Emilie Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Human Genome Research Institute (NHGRI), National Institute of Dental and Craniofacial Research (NIDCR), and Office of the Director (OD), National Center for Advancing Translational Sciences (NCATS) did not have any P grant spending between 2012 and 2020.

IC, Institutes and Centers; FY, Fiscal Year; NIAID, National Institute of Allergy and Infectious Diseases; NIAAMS, National Institute of Arthritis and Musculoskeletal and Skin Disorders; NCI, National Cancer Institute; NHLBI, National Heart, Lung, and Blood Institute; NIGMS, National Institute of General Medical Sciences; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NINDS, National Institute of Neurological Disorders and Stroke.

SOURCE: NIH, 2021f.

The committee reviewed NIH spending on autoimmune disease research by type of grant and type of research according to three categories: intramural, investigator-initiated, and solicited. As noted earlier, intramural research funding (Z) is for internal NIH investigator research activities, and R grant funding is the most common independent research grant mechanism. ICs use solicited research funding opportunities to support priority research areas. NIH communicates with the research community about these grant opportunities through a notice of special interest, program announcement, request for application, request for proposal, and other mechanisms. Figure 6-9<sup>6</sup> shows NIH funding for autoimmune disease research for the average over the study period and FY 2020. Of the three types of grants, investigator-initiated research grants received greater than 70 percent of the funding, however, funding for each type of research in FY 2020 is higher than the average over the study period. Table 6-7 shows funding of intramural, investigator-initiated, and solicited grants by ICs.

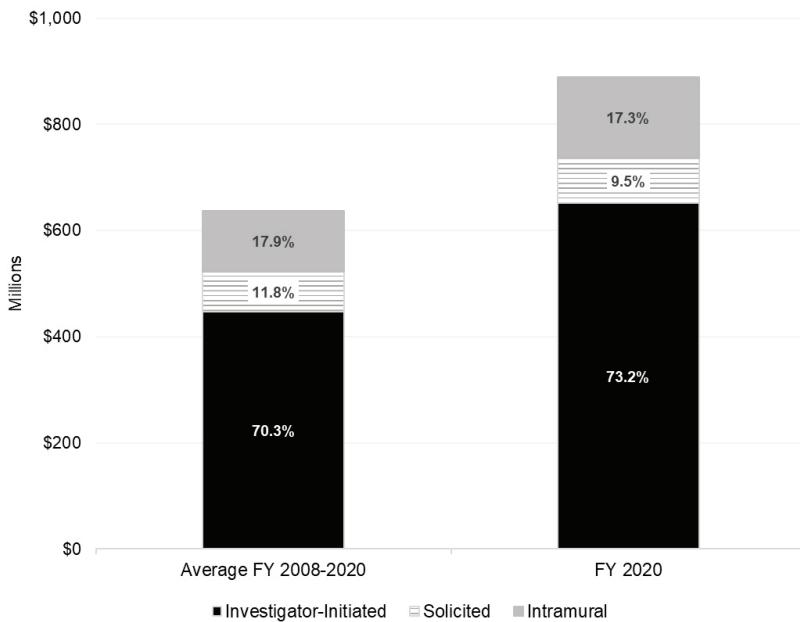
Funding for intramural research was highest for NIAID and NIAMS (about \$34 million each) in FY 2020 (Table 6-7).<sup>7</sup> NIAID and NIDDK had the highest level of funding for investigator-initiated research (\$187 million and \$185 million respectively), followed by NIAMS (\$86 million). NIDDK had the highest level of average FY 2008–2020 funding (\$127 million per year). Of the ICs reviewed, NIDDK also had the highest level of funding for solicited research grants. NIDDK solicited research funding was 2.7 times higher than NIAID funding for this grant type.

Intramural research activities represent 17.3 percent of NIH funding for autoimmune disease research in FY 2020. A total of 50 intramural principal investigators conduct autoimmune disease research, which may include basic, translational, and clinical studies. However, the committee notes that there is a relative lack of intramural principal investigators who focus on epidemiology and autoimmune diseases. The committee searched the NIH Intramural Research Program database<sup>8</sup> to identify principal investigators who conduct autoimmune disease research and principal investigators who engage in epidemiology-focused research (N=121). There are three intramural principal investigators who conduct research that overlaps both of these areas. This number is significantly lower than the number of principal investigators in the NCI intramural

<sup>6</sup> See Appendix G for methodology.

<sup>7</sup> See Appendix G for methodology.

<sup>8</sup> The committee used the NIH Intramural Research Program database available at <https://irp.nih.gov/our-research/principal-investigators/focus/epidemiology> (accessed January 7, 2022).



**FIGURE 6-9** NIH funding for autoimmune disease research for the average FY 2008–2020 and FY 2020.

NOTES: Autoimmune disease research categories were determined using Funding Opportunity Announcement (FOA) and Combined Total Cost of Funded Autoimmune Disease Research. Grants without an FOA were not included in the analysis. FY, fiscal year.

SOURCE: NIH, 2021f.

research program whose research focuses on both cancer and epidemiology (N=69).

### RESEARCH GRANTS BY AUTOIMMUNE DISEASE

NIH introduced the RCDC in 2009 to categorize funded research. RCDC categories include a research area, specific condition, or disease area, but the categories are not exhaustive or mutually exclusive (NIH, 2021a). Funded research as reported in NIH RePORTER may have multiple RCDC disease spending categories depending on the scientific and research focus of the project. Furthermore, diseases or conditions that do not have a specific RCDC spending category (diabetes mellitus type 1, antiphospholipid syndrome, Sjögren's disease, celiac disease, autoimmune thyroid disease, primary biliary cholangitis) must be searched for using "key terms," including the name of the condition and all iterations

**TABLE 6-7** Intramural, Investigator-Initiated, and Solicited Autoimmune Disease Research by IC, FY 2020 and Average FY 2008–2020

IC	Intramural		Investigator-Initiated		Solicited	
	FY 2020	Average FY 2008– 2020	FY 2020	Average FY 2008– 2020	FY 2020	Average FY 2008– 2020
NCI	\$14,270,000	\$10,882,000	\$11,684,000	\$10,347,000	\$9,416,000	\$2,074,000
NIAID	\$34,006,000	\$21,769,000	\$187,328,000	\$107,751,000	\$55,735,000	\$42,976,000
NHLBI	\$11,701,000	\$4,077,000	\$59,078,000	\$39,906,000	\$5,593,000	\$14,307,000
NIGMS	\$0	\$0	\$15,026,000	\$10,947,000	\$629,000	\$1,744,000
NINDS	\$13,474,000	\$9,765,000	\$54,562,000	\$50,127,000	\$11,350,000	\$3,113,000
NIDDK	\$7,566,000	\$4,921,000	\$185,951,000	\$127,257,000	\$153,690,000	\$120,316,000
NICHD	\$1,964,000	\$3,444,000	\$7,844,000	\$8,163,000	\$709,000	\$1,855,000
NIEHS	\$4,724,000	\$7,439,000	\$4,602,000	\$4,202,000	\$2,101,000	\$1,170,000
NCATS	\$2,606,000	\$1,564,000	\$590,000	\$472,000	\$2,801,000	\$2,801,000
NEI	\$14,983,000	\$9,614,000	\$18,624,000	\$10,587,000	\$376,000	\$128,000
NIAMS	\$35,790,000	\$28,182,000	\$86,159,000	\$72,297,000	\$25,767,000	\$20,573,000
NHGRI	\$7,003,000	\$3,945,000	\$65,000	\$371,000	\$3,401,000	\$6,688,000
NIDCR	\$4,930,000	\$7,740,000	\$13,950,000	\$6,191,000	\$0	\$1,350,000
OD	\$0	\$0	\$3,316,000	\$4,668,000	\$11,595,000	\$15,929,000

*continued*

**TABLE 6-7** Continued

NOTES: National Center for Advancing Translational Sciences (NCATS) average spending is from FY 2012 to 2020 autoimmune disease research categories were determined using funding opportunity announcement (FOA) and combined total cost of funded autoimmune disease research variables. Grants without an FOA were not included in the analysis. FY, fiscal year; IC, Institute or Center; NCI, National Cancer Institute; NEI, National Eye Institute; NHGRI, National Human Genome Research Institute; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIDCR, National Institute of Dental and Craniofacial Research; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS, National Institute of Environmental Health Sciences; NIGMS, National Institute of General Medical Sciences; NINDS, National Institute of Neurological Disorders and Stroke; OD, Office of the Director.

SOURCE: NIH, 2021f.

of it (e.g., names roughly equivalent to antiphospholipid syndrome include Hughes' syndrome, lupus anticoagulant, anticardiolipin, etc.).

The committee was interested in examining trends in the number of grants for autoimmune diseases of specific interest identified in Chapter 3. These diseases include inflammatory bowel disease (IBD), multiple sclerosis, type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's disease, psoriasis, celiac disease, autoimmune thyroid disease, antiphospholipid syndrome (APS), and primary biliary cholangitis (PBC). Hashimoto's disease and Grave's disease were combined into a single "autoimmune thyroid disease" category. In addition, grants that were not associated with the committee's specific disease categories or were not disease specific were labeled as "other autoimmune disease" throughout the analysis. RePORTER data includes funding information for each year of a grant (e.g., a 3-year R01 grant is identified as three increments of funding); the committee aggregated funding increments with the same grant number to represent one grant. In total, the committee identified and aggregated 28,148 funding increments into 8,470 autoimmune disease grants.<sup>9</sup> Figure 6-10 shows number of grants by disease category for FY 2008–2020.

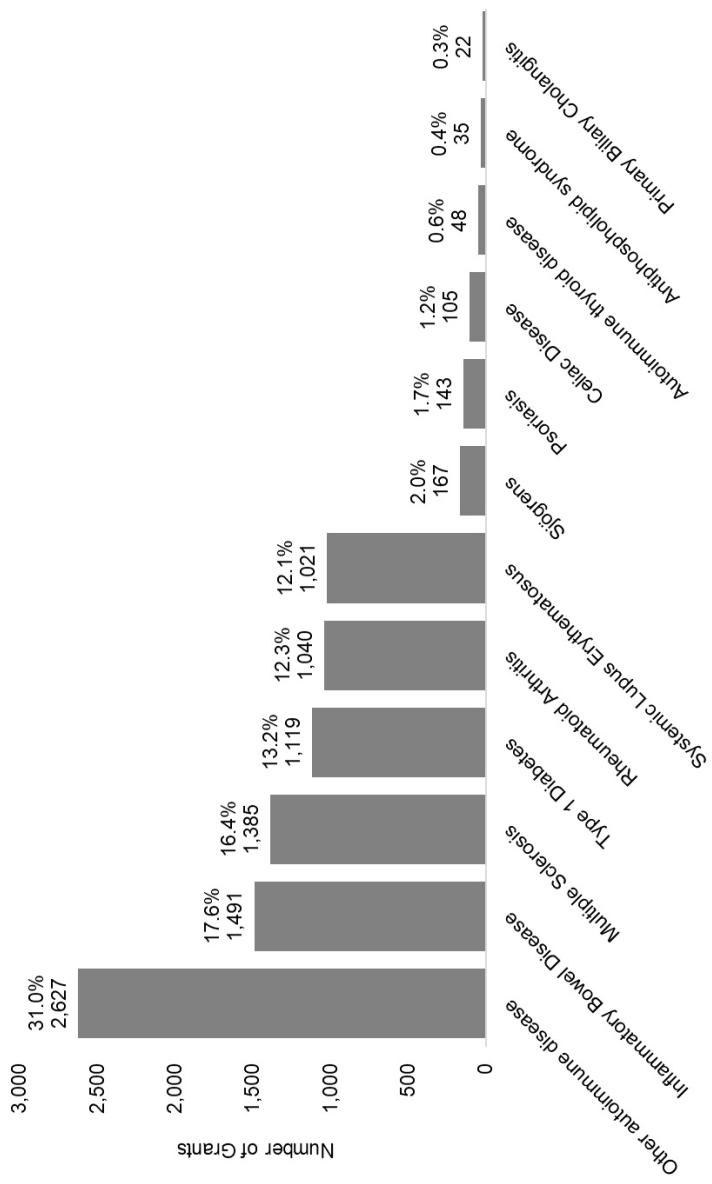
Of the autoimmune diseases the committee examined, the four diseases with the greatest number of funded grants over the FY 2008–2020 period were other autoimmune diseases (31.0 percent), IBD (17.6 percent), multiple sclerosis (16.4 percent) and type 1 diabetes (13.2 percent). Figure 6-11 shows the total number of grants by disease category funded by year, between 2008 and 2020. The number of IBD and type 1 diabetes grants increased gradually over time; multiple sclerosis grants declined after 2009. The number of other specific disease grants fluctuated over the period.

Autoimmune disease grants involved 98 distinct activity codes. Figure 6-12 shows the top 10 activity codes. Among these, R01 (35.9 percent) and R21 (12.4 percent) accounted for the largest number of grants. R01 grants are the standard investigator-initiated grants, and R21 grants are research exploratory/developmental grants meant to encourage the development of new research activities in specific program areas.

For R01 grants, other autoimmune disease (light purple) multiple sclerosis (dark purple), and IBD (yellow) were the most funded grants in FY 2020 (Figure 6-13). The number of grants increased for about half of the disease categories after 2016. IBD grants increased steadily over the period. Sjögren's disease, psoriasis, celiac disease, autoimmune thyroid disease, APS, and PBC had fewer than 25 grants per year.

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<sup>9</sup>Aggregated grants also include subprojects added to a parent project.



**FIGURE 6-10** Number of grants by disease category, FY 2008–2020 (N=8,470).

NOTES: Percentages in the figure sum to more than 100 percent because grants can be associated with more than one autoimmune disease. FY, fiscal year.

SOURCE: NIH, 2021f.

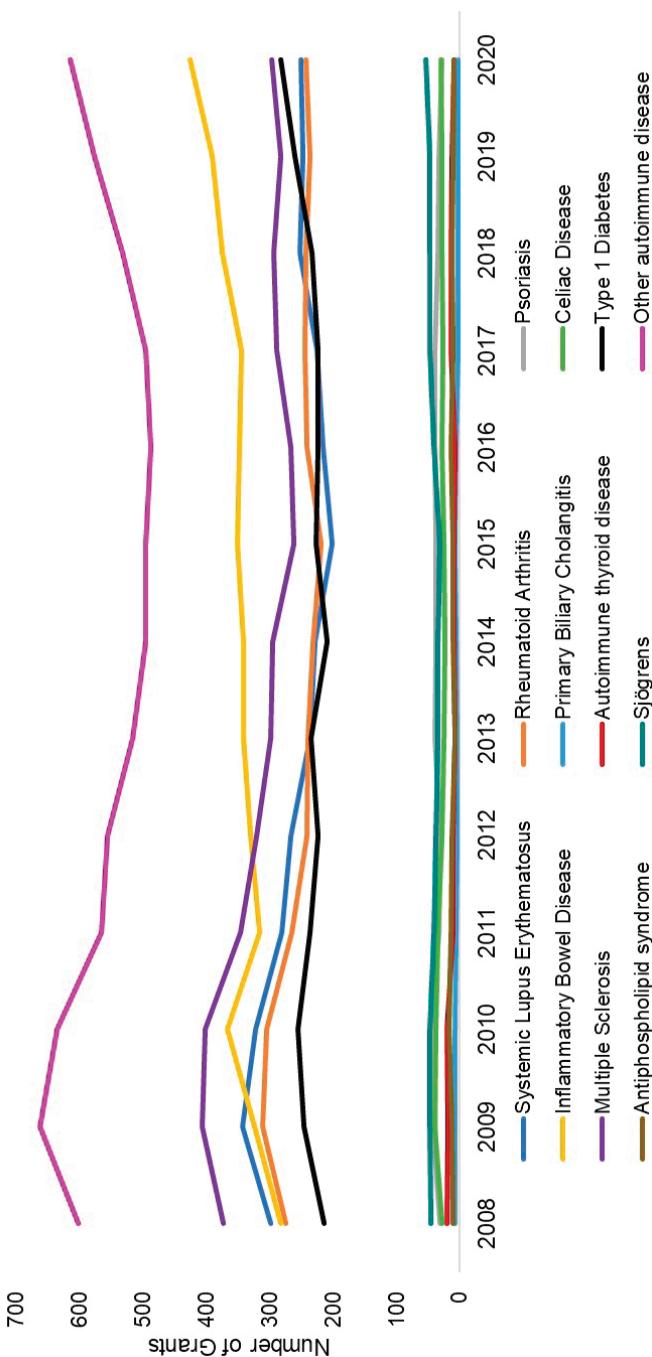


FIGURE 6-11

Number of autoimmune disease grants by disease, FY 2008–2020 (N=8,470).

NOTES: Percentages in the figure sum to more than 100 percent because grants can be associated with more than one autoimmune disease. FY, fiscal year.

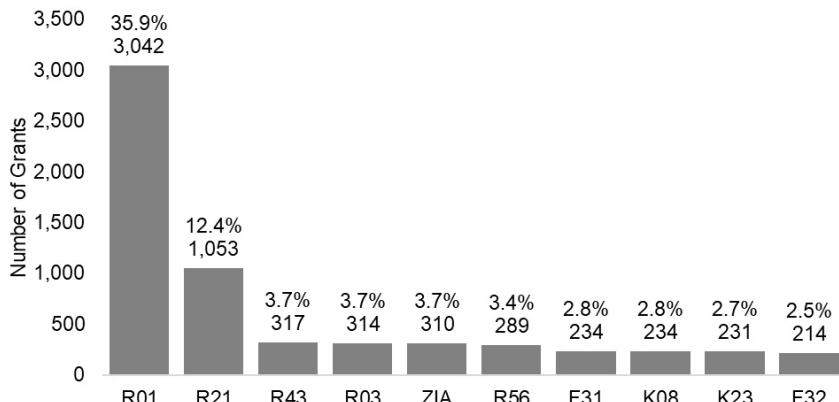
SOURCE: NIH, 2021f.

Among R01 research grants, non-competing continuation research grants (R01-5) were the most funded (32.5 percent) followed by new R01-1 grants (22.3 percent). Figure 6-14 shows the number of non-competing R01 grants by disease and Figure 6-15 shows new R01 grants by disease for FY 2008–2020. Non-competing continuation grants for all disease categories decreased in 2016 as a result of an administrative accounting change (Figure 6-15). There were no clear patterns in the trends in the number of new R01 grants funded by disease categories except for the increase in IBD grants over the study period.

The committee also examined the ICs designated as the funding IC for autoimmune disease grants (Figure 6-16). Among the top 10 funding ICs, NIDDK, NIAID, and NIAMS funded the largest number of grants.

Figures 6-17 through 6-19 show trends in autoimmune diseases by the top three funding ICs (NIDDK, NIAID, and NIAMS). Figure 6-17 shows that among NIDDK-funded grants, the disease categories with the greatest number of grants were IBD (yellow), type 1 diabetes (black), and other autoimmune disease (light purple).

Figure 6-18 shows NIAID-funded



**FIGURE 6-12** Top 10 activity codes for autoimmune disease research (N=8,470).  
 NOTE: R01 are the standard investigator-initiated grants, R21 are research exploratory or developmental grants for new research activities in categorical program areas, R43 are small business innovation research grants, R03 are small research grants for studies in categorical program areas. ZIA are intramural grants, R56 grants are for high-priority, short-term projects, F31 are fellowship grants, K08 are clinical investigator career development awards, K23 are mentored patient-oriented research career development grants, and F32 are postdoctoral individual national research service awards.

SOURCE: NIH, 2021f.

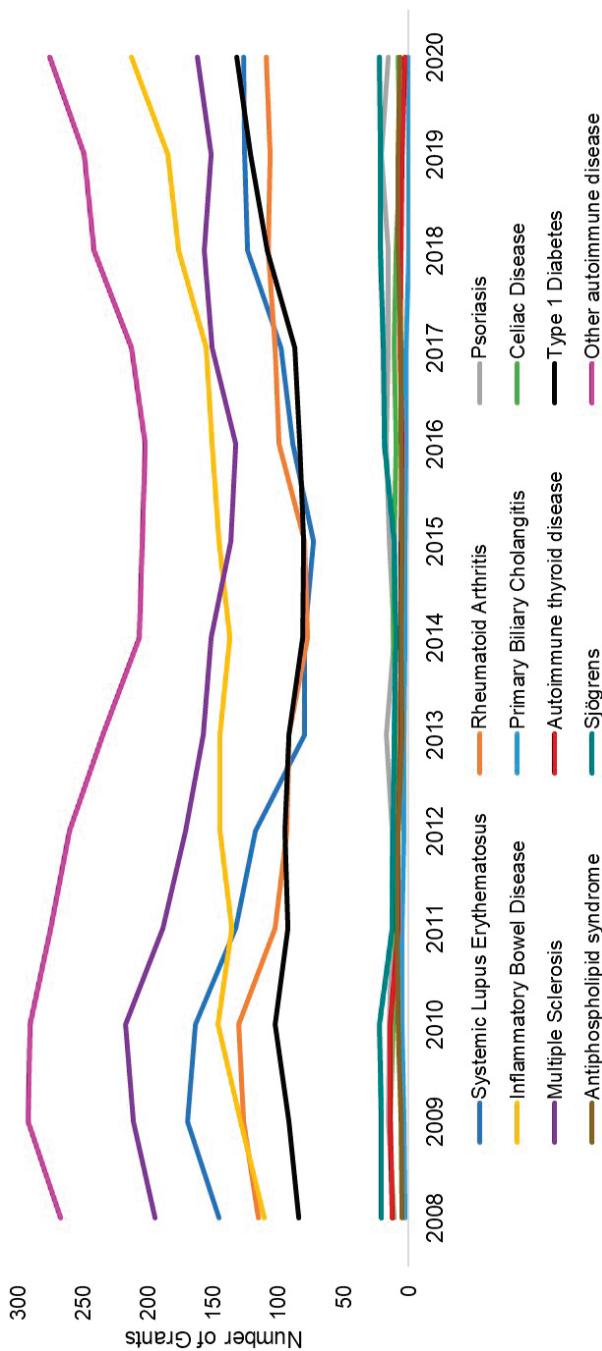
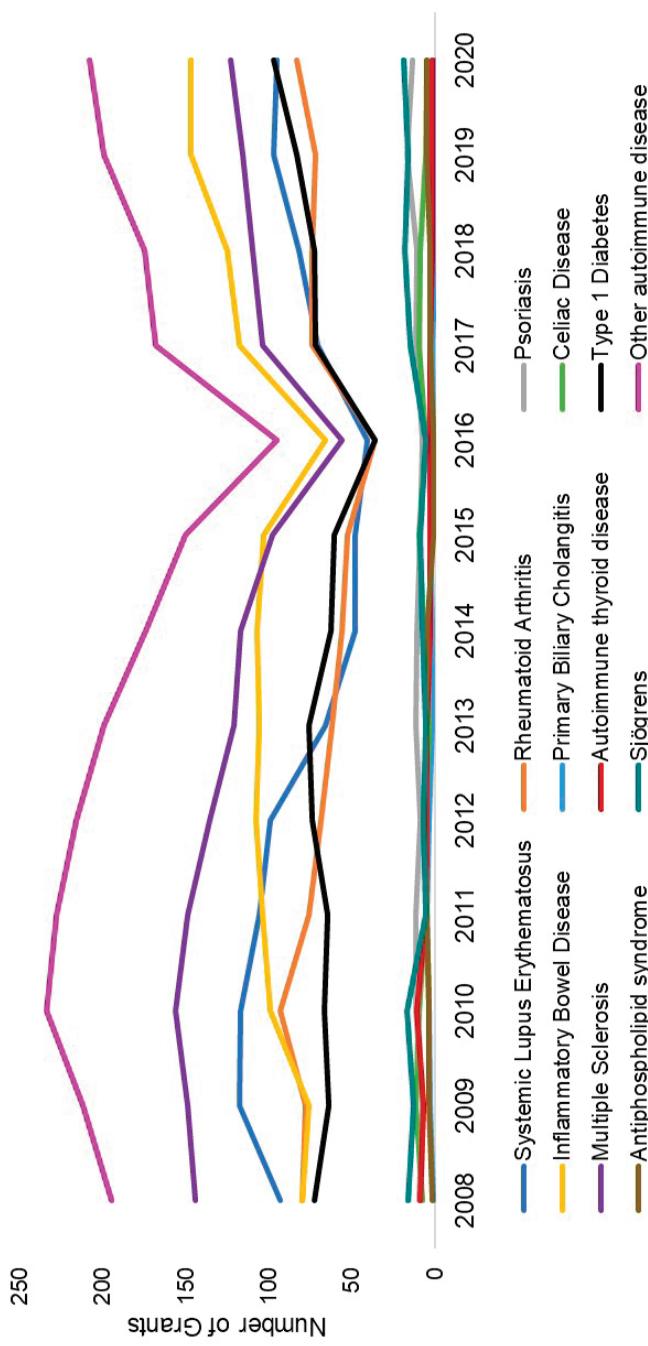


FIGURE 6-13 Number of R01 grants by autoimmune disease, FY 2008–2020 (N=3,042).

NOTE: FY, fiscal year.

SOURCE: NIH, 2021f.



**FIGURE 6-14** Number of non-competing continuation R01 grants by autoimmune disease, FY 2008–2020 (N=2,751).

NOTES: In FY 2014 and 2015, non-competing awards were issued as extension awards to support NIH's transition to Payment Management System subaccounts. The decrease in non-competing continuation R01 grants in 2016 is related to this accounting change. FY fiscal year.

SOURCE: NIH, 2021f.

grants by disease. The top three disease categories with the most grants were other autoimmune diseases (light purple), SLE (dark blue), and multiple sclerosis (dark purple). While NIAID-funded IBD grants (yellow) seemed to increase steadily since 2011, SLE and multiple sclerosis grants decreased in 2015 but have since increased. Figure 6-19 shows NIAMS-funded grants by disease. The top three disease categories with the most grants were rheumatoid arthritis (orange), other autoimmune diseases (light purple), and SLE (dark blue).

### IC Collaboration on Research Funding Opportunities

ICs can take steps among themselves to coordinate their research interests and to leverage their mutual expertise and resources.<sup>10</sup> One measure of collaboration is the degree to which ICs engage in joint funding of specific autoimmune diseases research activities. To assess the level of collaboration among ICs, the committee examined co-funded autoimmune disease research grants for FY 2008–2020. To accomplish this, the committee used NIH RePORTER data to identify administrative ICs funding autoimmune disease research grants and corresponding funding ICs that contributed to the total cost of grants during this period.

All 14 ICs collaborated with other ICs<sup>11</sup> to co-fund autoimmune disease research activities during the period. Among the large ICs, NIAID (4.23), NHLBI (2.70), and NIDDK (2.62) had the largest average number of joint IC funding collaborations (Table 6-8).<sup>12</sup> These ICs jointly funded research grants with one to six other ICs in a given year and collaborated with eight to nine different ICs over the period. NIDDK collaborated consistently with at least one IC each year and with up to six ICs during a given year. Among the smaller ICs, NIAMS (3.4) had the highest average number of joint IC funding collaborations followed by NIDCR (1.10) and NCATS (1.00). NIAMS collaborated with nine different ICs over the period. NIDCR and NCATS collaborated with four and three different ICs (respectively) during the period. Most collaborations were on P, R, and U grants.

<sup>10</sup> According to multiple NIH speakers who spoke at the committee's public information-gathering sessions (Goldmuntz, 2020; Hodge, 2021; McNamara, 2021).

<sup>11</sup> ICs of the committee's focus.

<sup>12</sup> See Appendix G for methodology.

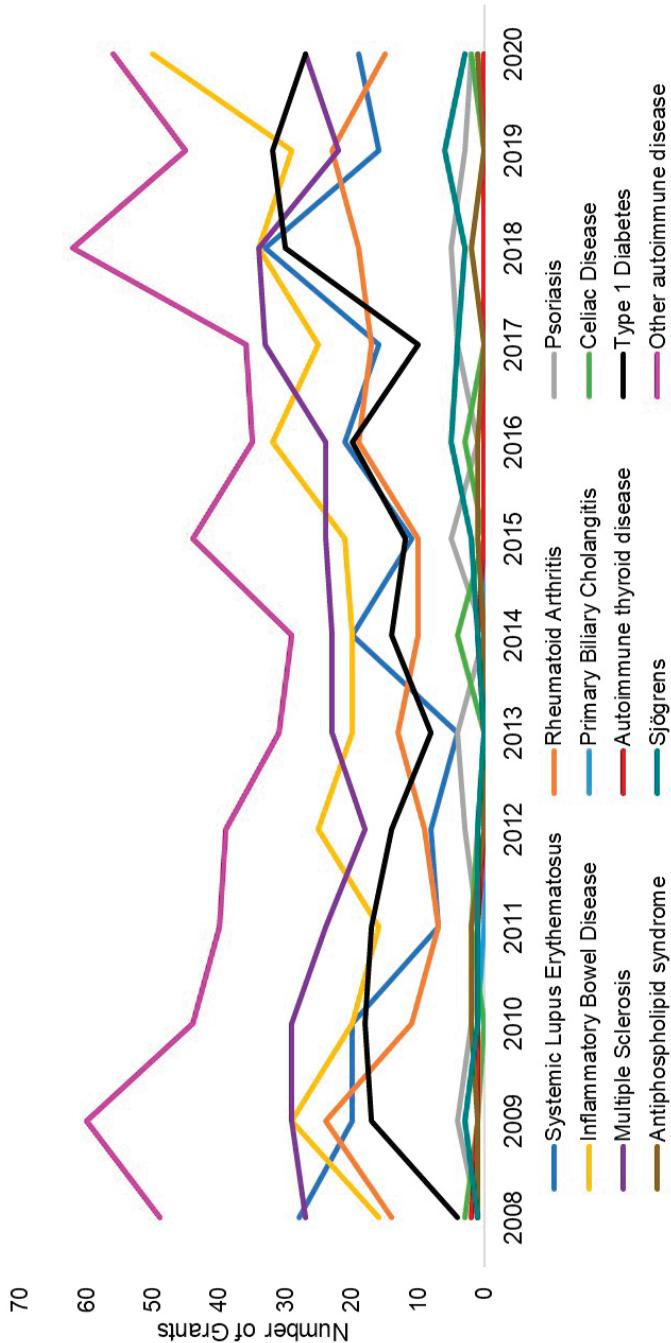
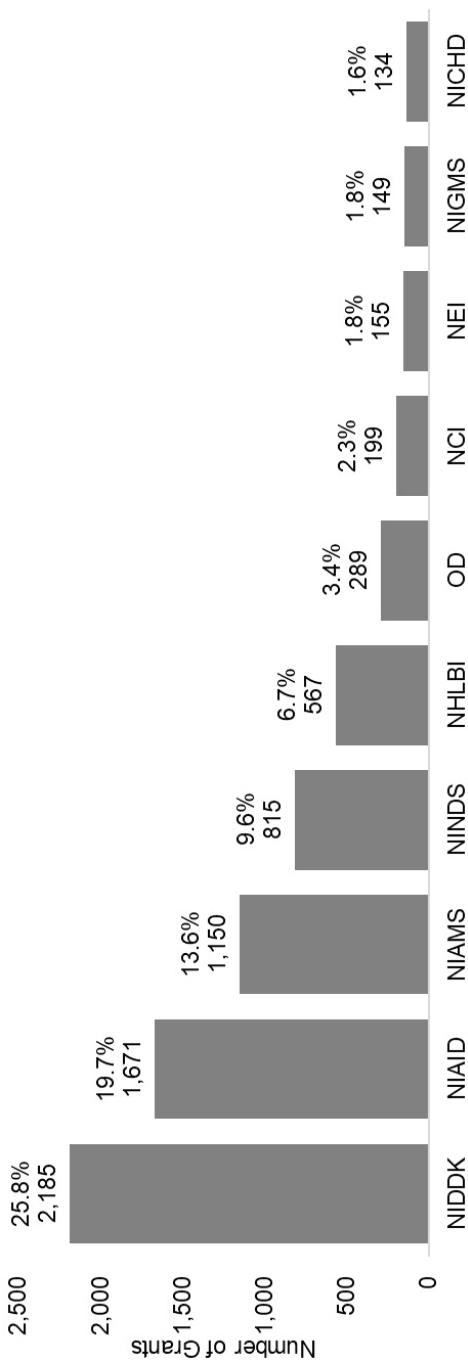


FIGURE 6-15 New R01 grants by autoimmune disease, FY 2008–2020 (N=1,892).

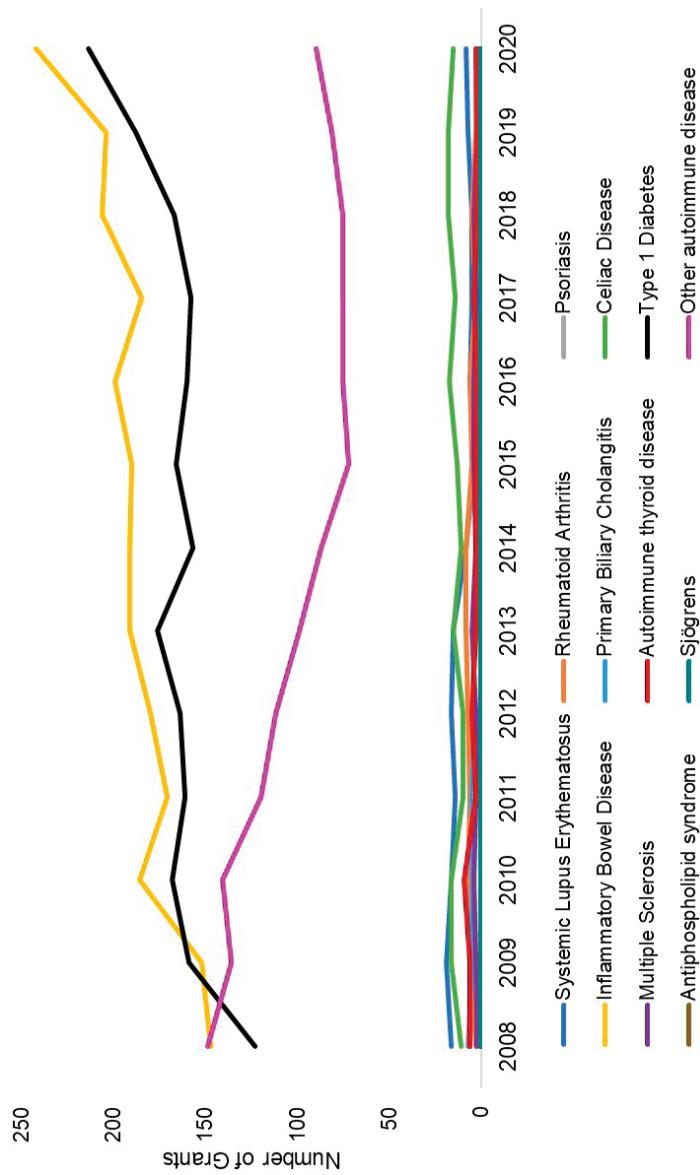
NOTE: FY, fiscal year.  
SOURCE: NIH, 2021f.



**FIGURE 6-16** Top 10 funding ICs by grants, FY 2008–2020 (N=8,470).

NOTES: Percentages do not sum to 100 percent because the figure includes only the top 10 funding ICs and does not include grants without a funding IC listed in NIH RePORTER. FY, fiscal year; IC, Institute or Center.

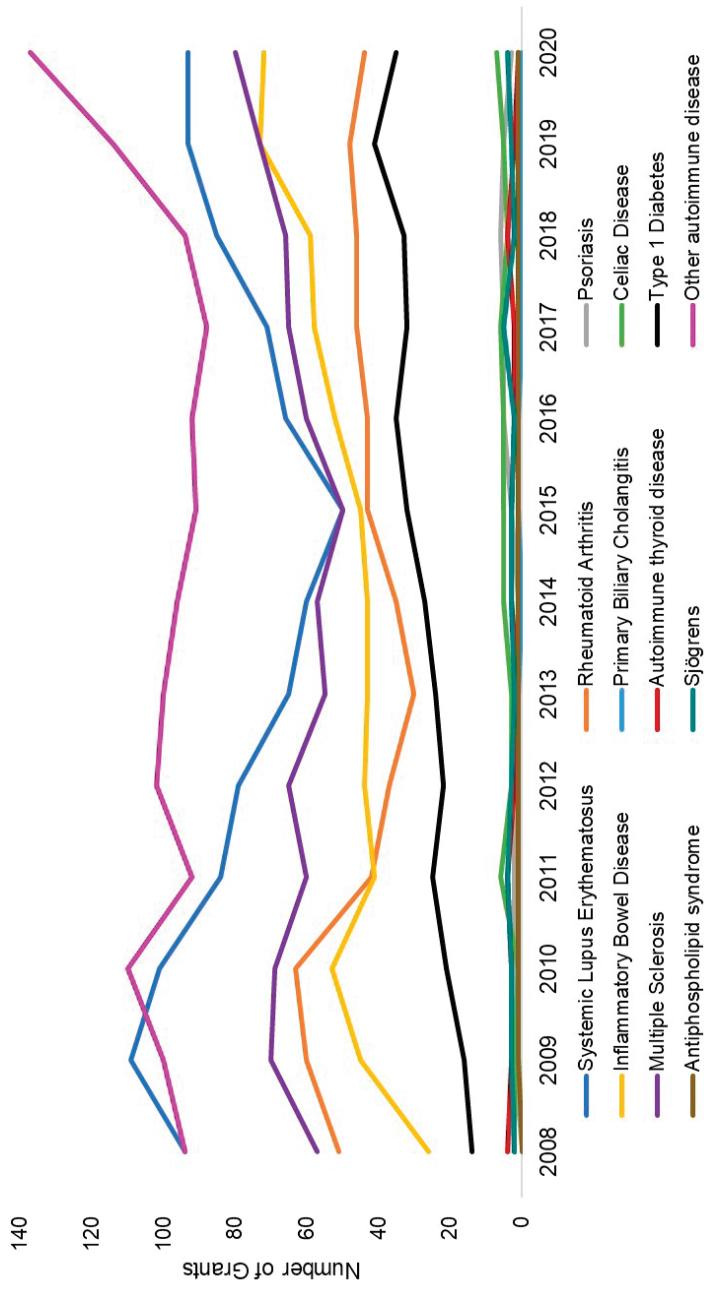
SOURCE: NIH, 2021f.



**FIGURE 6-17** NIDDK (funding IC) grants by disease, FY 2008–2020 (N=2,185).

NOTES: This graph represents the number of grants with NIDDK funding. NIDDK was not necessarily the sole funder of each grant. FY, fiscal year; IC, Institute or Center; NIDDK, National Institute of Diabetes and Digestive Kidney Diseases.

SOURCE: NIH, 2021f.

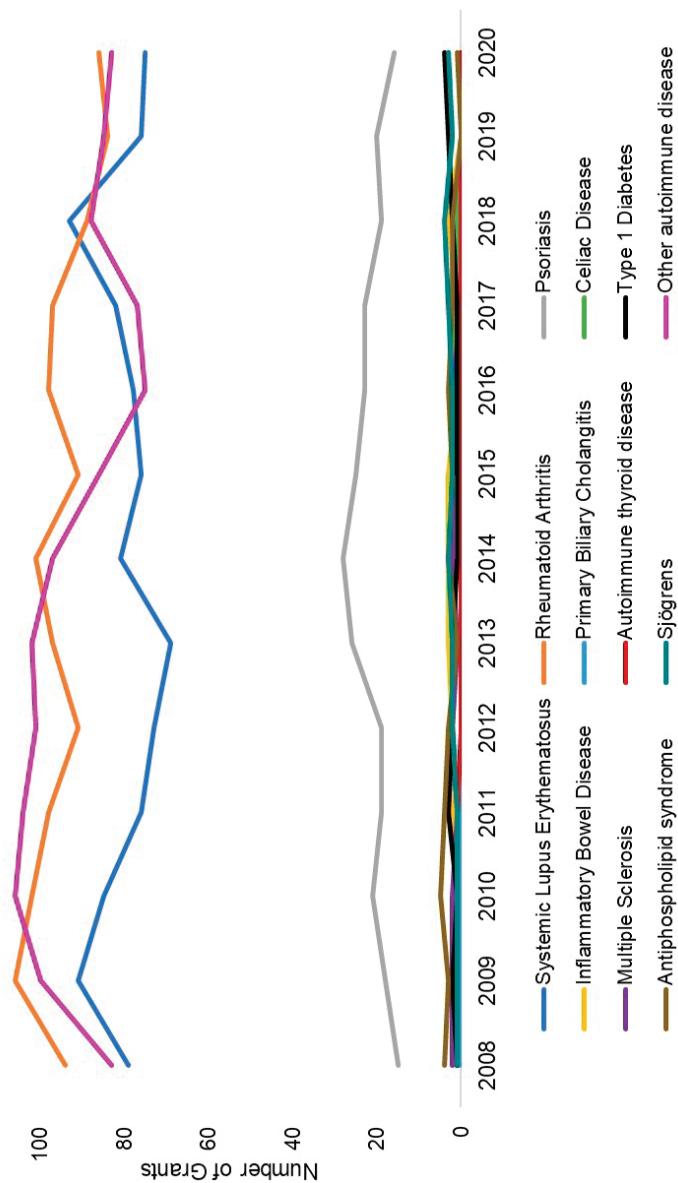


**FIGURE 6-18** NIAID (funding IC) grants by disease, FY 2008–2020 (N=1,671).

NOTES: This graph represents the number of grants with NIAID funding. NIAID was not necessarily the sole funder of each grant.

FY, fiscal year; IC, Institute or Center; NIAID, National Institute of Allergy and Infectious Diseases.

SOURCE: NIH, 2021f.



**FIGURE 6-19** NIAMS (funding IC) grants by disease, FY 2008–2020 (N=1,150).  
 NOTES: This graph represents the number of grants with NIAMS funding. NIAMS was not necessarily the sole funder of each grant. FY, fiscal year; IC, Institute or Center; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases.  
 SOURCE: NIH, 2021f.

## RESEARCH FOCUS OF FUNDED GRANTS

The statement of task directed the committee to evaluate the NIH research portfolio with particular attention to issues such as risk factors, diagnostic tools, barriers to diagnoses, treatments, and prospects for cures. Given the enormity of the task, which would have required that the committee review the 8,470 abstracts associated with the autoimmune disease grants funded from 2008 to 2020, the committee found three ways to approach the task in a more efficient and manageable way. The first approach used research topic modeling, a type of statistical modeling to identify popular “topics” that appeared in the abstracts. In the second approach, committee members utilized RCDC spending categories and RePORTER data to determine which particular spending categories were co-occurring with the autoimmune disease spending category. In the third approach, the committee reviewed a sample of research grant abstracts to identify the primary focus of the research.

The committee, with the aid of a consultant, used latent dirichlet allocation (LDA) statistical modeling to identify research topics in the set of 8,470 NIH research abstracts related to autoimmune disease grants funded between 2008 and 2020. Topic modeling using LDA is a method of fitting a pre-determined number of topics to a set of texts. The LDA algorithm repeatedly selects and assigns words in each document to a topic and assesses the “fit” of the word to the topic by looking at what words are frequently found together across the texts (Blei et al., 2003). In the past, researchers have applied LDA modeling to scientific abstracts to analyze funding patterns and trends in research (Park et al., 2016; Porturas and Taylor, 2021). Based on the coherence score of words<sup>13</sup> that tended to co-occur together in the dataset, 30 topics were determined to be the optimal number of topics that could be used to fit the data (words) in the abstracts (Bittermann and Fischer, 2018; Park et al., 2016; Porturas and Taylor, 2021). See Appendix H for more detailed information.

One of the outputs of the LDA model is a matrix that shows the proportion of topics assigned to each abstract. For example, 30 percent of the words in an abstract might belong to topic 1, and 70 percent of words in an abstract might belong to topic 2. The topic with the highest proportion within each abstract was assigned to the abstract. Topics were combined

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<sup>13</sup> Coherence score is a score that calculates whether the words in the same topic make sense when they are grouped together and is an indicator of the quality of the topics being produced (Cristian, 2020).

**TABLE 6-8** IC Collaboration, FY 2008–2020

Large ICs			
IC	Average Number of Joint IC Funding Collaboration (2008–2020)	Range of Joint IC Funding Collaboration per Year	Number of Collaborating ICs (2008–2020)
NCI	1.38	0-4	4
NIAID	4.23	3-6	8
NHLBI	2.70	1-5	9
NIGMS	1.77	0-4	5
NINDS	1.62	0-3	7
NIDDK	2.62	1-4	8
NICHD	2.00	1-3	5
Small ICs			
IC	Average Number of Joint IC Funding Collaboration (2008–2020)	Range of Joint IC Funding Collaboration per Year	Number of Collaborating ICs (2008–2020)
NIEHS	0.54	0-1	1
NCATS	1.00	1-3	3
NEI	0.23	0-1	1
NIAMS	3.54	1-6	9
NHGRI	0.38	0-1	2
NIDCR	1.10	0-2	4
OD	0.46	0-1	2

NOTES: Large ICs have FY 2020 actual total obligations greater than \$1 billion, and small ICs have actual total obligations of less than \$1 billion. All ICs in this table are administrative ICs. FY, fiscal year; IC, Institute or Center; NCATS, National Center for Advancing Translational Sciences; NCI, National Cancer Institute; NEI, National Eye Institute; NHGRI, National Human Genome Research Institute; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NIDCR, National Institute of Dental and Craniofacial Research; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS, National Institute of Environmental Health Sciences; NIGMS, National Institute of General Medical Sciences; NINDS, National Institute of Neurological Disorders and Stroke; OD, Office of the Director.

SOURCE: NIH, 2021f.

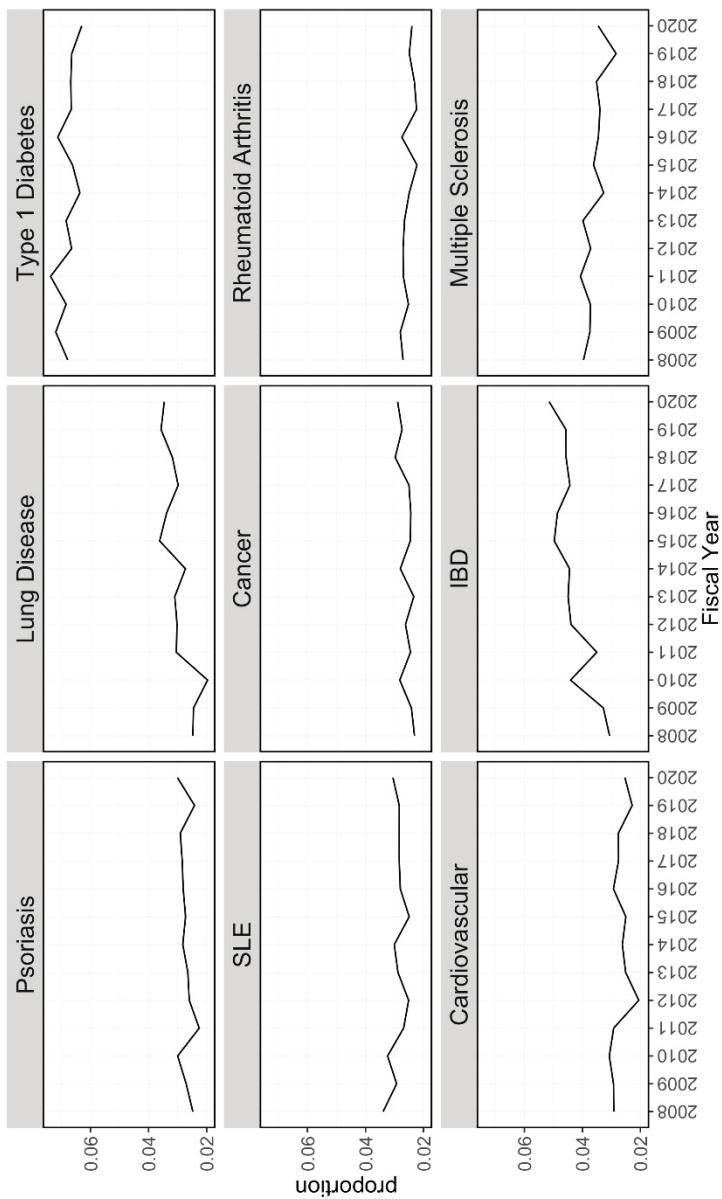
**BOX 6-1**  
**LDA-Derived Topics Based on 8,470**  
**Autoimmune Disease Grants**

Disease Focused Topics	Immune Response Related Topics	Clinical Topics	Administrative Topics
Psoriasis Lung Disease Type 1 Diabetes SLE Cancer Rheumatoid Arthritis Cardiovascular IBD Multiple Sclerosis	Immune response (innate immunity) Other (non-antibody) mechanisms of adaptive immunity Animal model Gene expression Epithelial Barrier Genetics Pathogenesis Virus (infectious etiology)	Treatment/ Therapy Disease progression Diagnostic Imaging	Centers/Core Projects Funding Training (funding)

NOTE: SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease.

based on similarity of words within topics. Box 6-1 shows the final list of 23 topics that fit the data the best.

Figures 6-20 through 6-23 show the frequency of these topic assignments from 2008 to 2020. This graphic is a depiction of the popularity of the research topics in the grants over the period. Trends over time show that the research topics related to IBD, treatment/therapy, lung disease, diagnostic [tools], and imaging have trended upward in contrast to animal model, genetics, and pathogenesis. Compared to the other disease focused topics, type 1 diabetes was prevalent among grants over time (Figure 6-20). Cancer, rheumatoid arthritis, cardiovascular, and multiple sclerosis remained consistent over the time period. In Figure 6-21, immune response (innate immunity) may be disproportionately high because of its relevance to various aspects of autoimmune disease research as well as a lack of a concrete definition for innate immunity. Between 2008 and 2018, the mention of treatment/therapy in autoimmune disease grant abstracts drastically increased, but then decreased sharply (Figure 6-22). However, mention of disease progression, diagnostic, and imaging generally increased during the latter part of the decade. In Figure 6-23, centers/



**FIGURE 6-20** LDA-generated topics for NIH autoimmune disease grants, FY 2008–2020: Disease focused topics.  
 NOTE: IBD, inflammatory bowel disease; LDA, latent dirichlet allocation; SLE, systemic lupus erythematosus.  
 SOURCE: NIH, 2021f.

core project funding was variable throughout the time period, and there has been a consistent decrease in the mention of training being present in autoimmune disease abstracts, especially between 2015 and 2020.

One of the downsides of using LDA for topic modeling is that the topics must be discovered “latent” within the texts and cannot be inputted into the model algorithm. In other words, this method cannot be used to actively search for specific research topics.

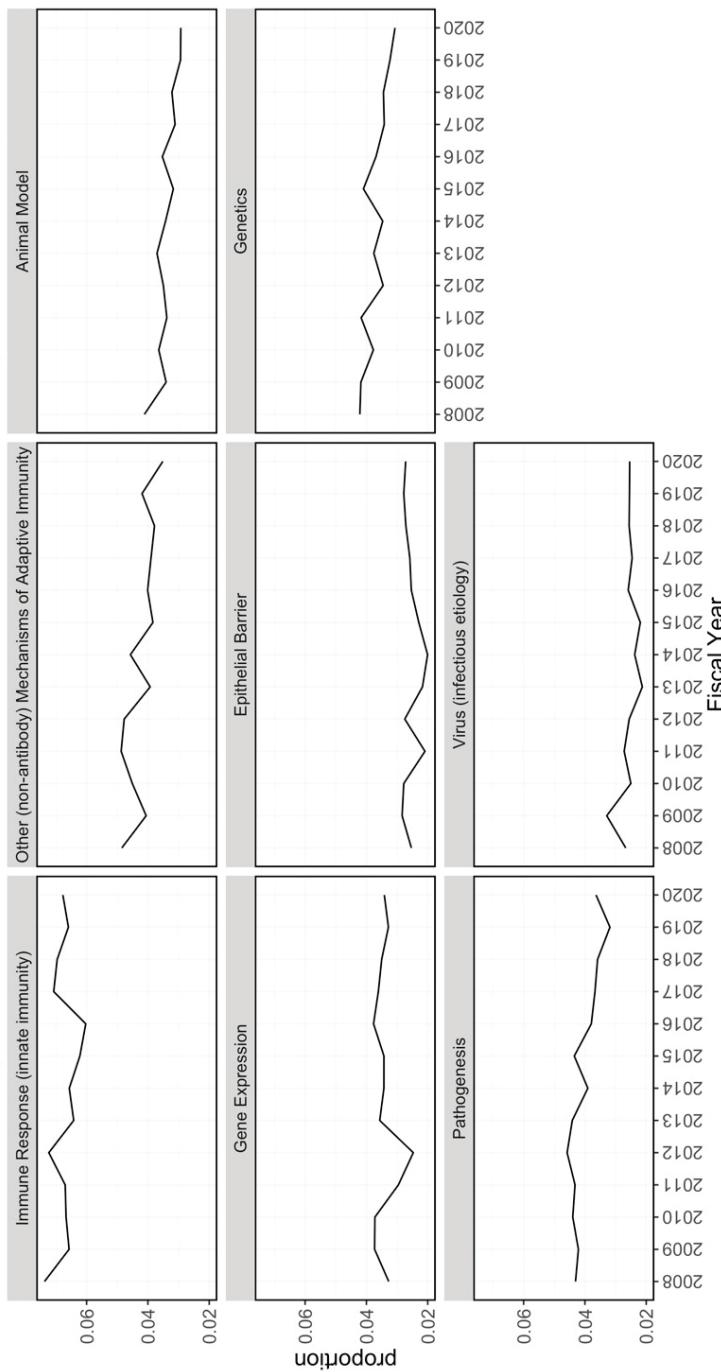
### RCDC Spending Categories

The second approach the committee used to evaluate the NIH research portfolio was to determine which other NIH RCDC spending categories co-occur with the autoimmune disease spending category. This can provide insight into themes within NIH’s autoimmune disease research portfolio. The definitions of the categories include all aspects of the topic, including basic, pre-clinical, clinical, biomedical, health services, behavioral, and social research, as defined by NIH scientific experts (NIH, 2020a). However, the definitions are not publicized. Table 6-9 shows the RCDC spending categories that the committee selected for analysis based on the statement of task, concepts, or conditions known to be related to autoimmune disease, and affected populations. Out of the 25 RCDC spending categories the committee analyzed, Genetics (32.1 percent), Biotechnology (23.4 percent), Prevention (22.9 percent), Pediatric (15.9 percent), and Women’s Health (12.9 percent) were the top five spending categories co-occurring with the autoimmune disease spending category in a total of 8,470 grants.

### PICO Portal

PICO Portal is an online tool used to review and manually categorize scientific literature. Given the large variation in the number of grants per disease, the committee decided to take random, weighted samples of the selected diseases as follows: a 10 percent sample of diseases with greater than 1,000 grants (“other autoimmune disease,” IBD, multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and SLE), a 50 percent sample of diseases between 100 and 999 grants (Sjögren’s, psoriasis, and celiac disease), and a 100 percent sample of diseases with fewer than 99 grants APS (autoimmune thyroid disease and PBC). This resulted in a total of 1,148 grants. Grants were then deduplicated (because a grant could have been assigned to more than one disease), resulting in a total of 1,127 grants for the committee to manually categorize. 1,127 is approximately 13 percent of the total number of grants (N=8,470).

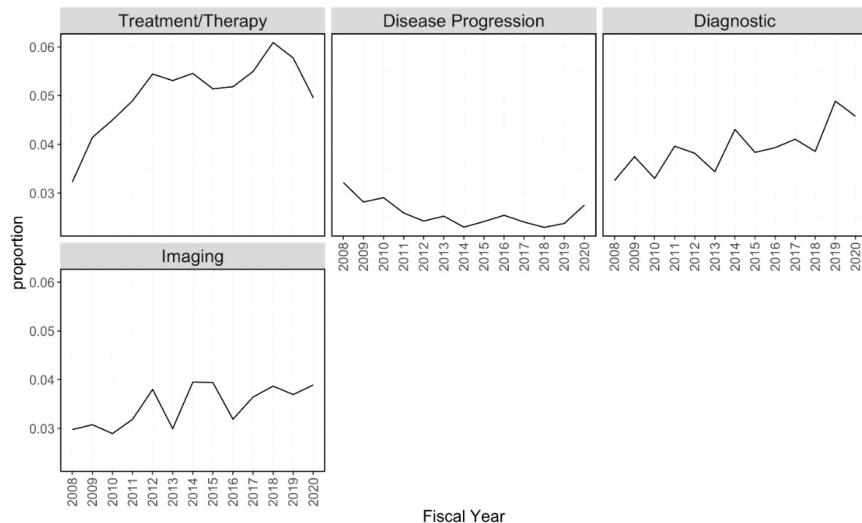
Research characteristics were chosen to evaluate the portfolio and identify the focus of the research. These characteristics encompass various



**FIGURE 6-21** LDA-generated topics for NIH autoimmune disease grants, FY 2008–2020: Immune response related topics.

NOTE: FY, fiscal year; LDA, latent dirichlet allocation.

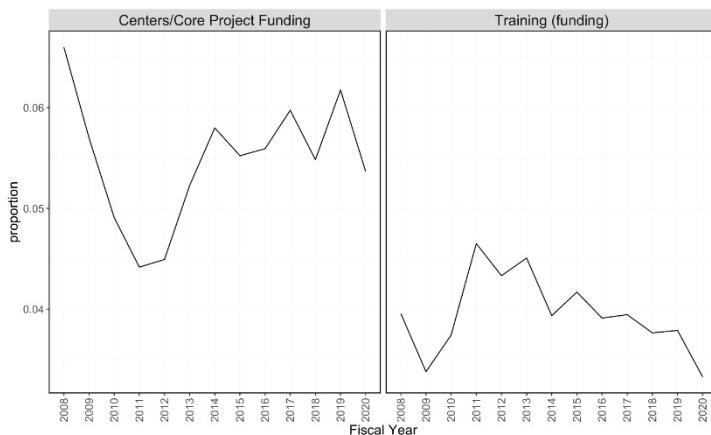
SOURCE: NIH, 2021f.



**FIGURE 6-22** LDA-generated topics for NIH autoimmune disease grants, FY 2008–2020: Clinical topics.

NOTE: FY, fiscal year; LDA, latent dirichlet allocation.

SOURCE: NIH, 2021f.



**FIGURE 6-23** LDA-generated topics for NIH autoimmune disease grants, FY 2008–2020: Administrative topics.

NOTE: FY, fiscal year; LDA, latent dirichlet allocation.

SOURCE: NIH, 2021f.

**TABLE 6-9** Percent of Autoimmune Disease Grants Co-occurring with other RCDC Spending Categories (N=8,470)

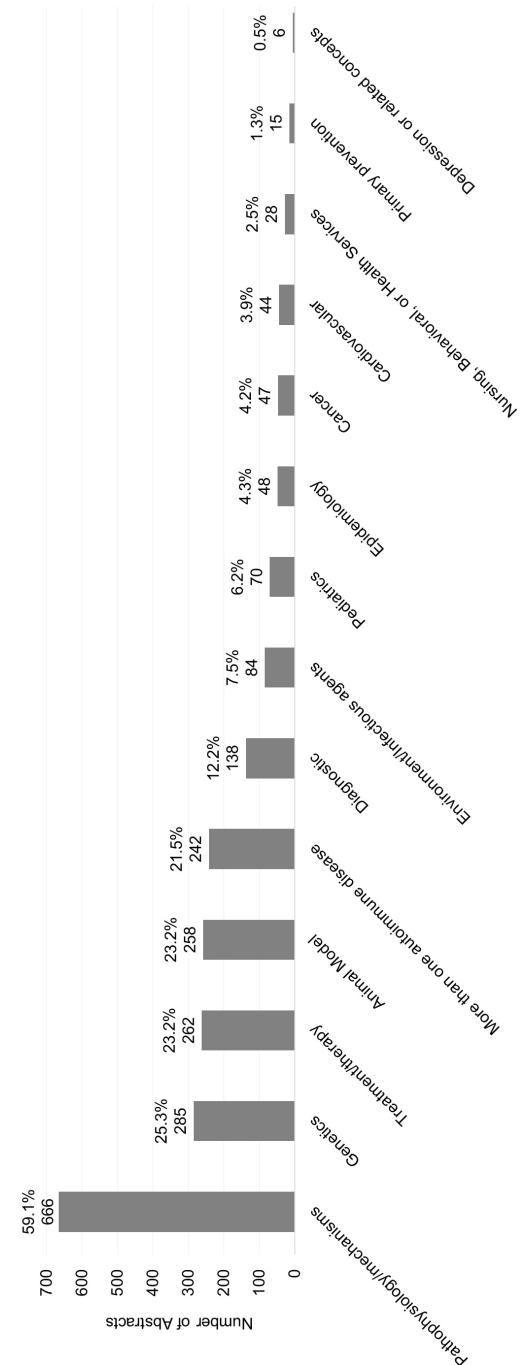
RCDC Spending Category	Co-Occurring with Autoimmune Disease Spending Category	
Genetics	2,718	32.1%
Biotechnology	1,978	23.4%
Prevention	1,938	22.9%
Pediatric	1,349	15.9%
Women's Health	1,095	12.9%
Infectious Disease	1,007	11.9%
Aging	688	8.1%
Cancer	660	7.8%
Minority Health	590	7.0%
Cardiovascular	490	5.8%
Immunotherapy	388	4.6%
Eye Disease and Disorders of Vision	327	3.9%
Microbiome	298	3.5%
Biomedical Imaging	176	2.1%
Precision Medicine	157	1.9%
Pain Research	143	1.7%
Health Services	132	1.6%
Estrogen	71	0.8%
Chronic Pain	56	0.7%
Acquired Cognitive Impairment	49	0.6%
Depression	42	0.5%
Cerebrovascular	41	0.5%
Fibromyalgia	14	0.2%
Burden of Illness	12	0.1%
Caregiving Research	2	0.0%

SOURCE: NIH, 2021f.

concepts in the statement of task, co-morbid diseases or complications of autoimmune disease, and type and method of research. Examining more than one autoimmune disease aimed to capture grants exploring the co-occurrence of autoimmune diseases. Within PICO Portal, the committee used the tagging feature to categorize the abstracts with one or more of the following research characteristics: animal model, cancer, cardiovascular, depression, diagnostic, environment/infectious agents, epidemiology, genetics, nursing/behavioral health services, pathophysiology/mechanisms, pediatrics, primary prevention, treatment/therapy, in vivo human study, in vivo animal study, in vitro study, and more than one autoimmune disease. The committee predefined specific definitions of the research characteristics in order to tag abstracts objectively.

Figures 6-24 and 6-25 show the number and percentage of abstracts tagged with the research characteristics. More than half (59.1 percent) of the 1,127 abstracts were tagged as having a focus on pathophysiology/mechanisms, followed by genetics (25.3 percent), treatment/therapy (23.2 percent), and animal model (23.2 percent). “Animal model” refers to the development of a new in vivo animal study for use to study autoimmune disease, whereas “in vivo animal study” refers to the use of an already existing animal model. Approximately 22 percent of the abstracts mentioned or focused on more than one autoimmune disease. In addition, the committee tagged abstracts based on the type of study researchers intended to conduct with their grant funding (Figure 6-25). Almost half of the abstracts were identified as being an in vivo animal study (48.4 percent), followed by in vitro (40.8 percent), and in vivo human study (29.3 percent).

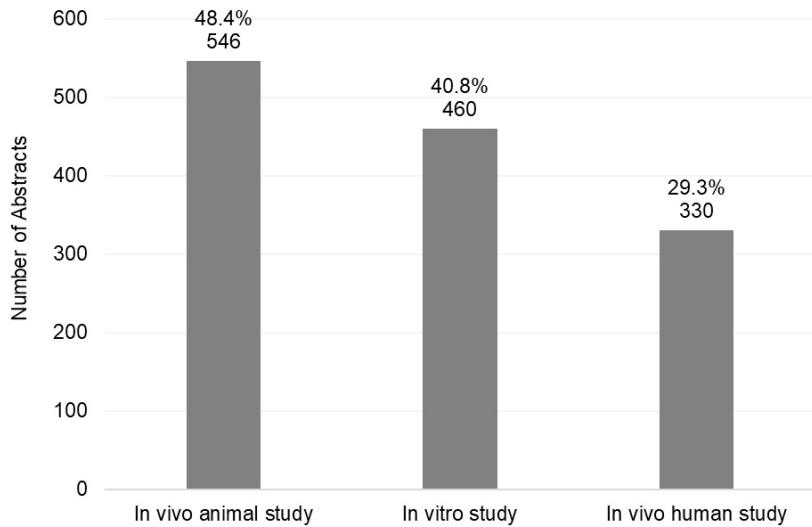
It is important to note the discrepancy between the RCDC spending category “prevention” and “primary prevention” as a predefined research characteristic tag in PICO Portal. The committee defined primary prevention, found in 1.3 percent of abstracts, as “research that focuses on preventing an autoimmune disease from occurring in an individual,” and is only one of the three levels of prevention. In contrast, almost one-third of autoimmune disease grants included the RCDC prevention category, suggesting that RCDC may use a different definition that includes other levels of prevention. Alternatively, depression as both an RCDC category and a PICO Portal research characteristic tag both occurred infrequently in autoimmune disease grants (0.5 percent). This points to a potential opportunity to explore depression as a disease that coincides with autoimmune disease.



**FIGURE 6-24** Research characteristics identified within autoimmune disease grant abstracts (N=1,127).

NOTE: Percentages in the figure sum to more than 100 percent because grants could be tagged with more than one research characteristic.

SOURCE: NIH, 2021f.



**FIGURE 6-25** Type of studies identified within autoimmune disease grant abstracts (N=1,127).

NOTE: Percentages in the figure sum to more than 100 percent because grants could be tagged with more than one research characteristic.

SOURCE: NIH, 2021f.

### Study Section Analysis

Investigator-initiated research (R01) grants are the most common research grants funded (Figure 6-9). As noted in Chapter 5, study sections review applications for these grants, with study section peer reviewers responsible for assigning priority scores based on scientific merit. Peer reviewers draw upon their expertise in investigating line(s) of research comparable to those under review to assign scores that distinguish the very best applications from the weaker ones.

The committee used the NIH Center for Scientific Review (CSR) study section search tool to analyze study sections that review R01 grant applications.<sup>14</sup> As many as 100 different study sections may be involved in

<sup>14</sup> The committee used the online CSR study section tool available at <https://public.csr.nih.gov/StudySections>, accessed November 24, 2021. The committee entered the name of each of the select autoimmune diseases of committee interest into the study section search field to identify the names of its associated chartered study sections.

Only chartered study sections were included because they review most investigator-initiated research grant applications. The total number of chartered study sections for all select diseases (de-duplicated) was then tallied.

reviewing unsolicited investigator-initiated research grant applications focusing on the select autoimmune diseases the committee chose to examine. Given that such a large number of diverse study sections can potentially review autoimmune disease grant applications, CSR should ensure that individual study section rosters include the appropriate expertise, including expertise for reviewing animal and human studies, to provide the proper review of these applications.

Table 6-10<sup>15</sup> provides a snapshot of data generated by the RePORTER Matchmaker tool. The table shows study sections—the names of which appear in the far left column—that reviewed funded grants focusing on the autoimmune diseases of interest to the committee; the table reflects a 2-year period.<sup>16,17</sup> The table identifies those study sections that reviewed the most funded grants for each disease of focus according to a bar graph RePORTER automatically generates to provide this information; the number of grants are indicated in the corresponding cells. One to three study sections reviewed the majority of funded grants for the two years, suggesting that this more limited number of study sections has the correct expertise for review of autoimmune disease grant applications. The committee notes that a more valuable analysis would have been to identify, for a given period, the grant applications that were reviewed for the select diseases regardless of whether they were approved. This would have provided a better baseline for analyzing patterns of review by the study sections. However this information was not available. The most common study sections responsible for the grant applications in this analysis were Gastrointestinal Mucosal Pathobiology; Hypersensitivity, Autoimmune and Immune-Mediated Diseases; Arthritis, Connective Tissue and Skin; Oral, Dental and Craniofacial Science; Cellular and Molecular Immunology B; Clinical Neuroimmunology and Brain Tumor; Innate Immunity and Inflammation; Cellular and Molecular Biology of Glia; Clinical and Integrative Diabetes and Obesity; Cellular Aspects of Obesity and Diabetes; and Hepatobiliary Pathophysiology.

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<sup>15</sup> See Appendix G for methodology.

<sup>16</sup> The committee used the RePORTER Matchmaker search tool available at <https://reporter.nih.gov/matchmaker>, accessed December 3, 2021. The committee entered the name of each of the select autoimmune diseases of committee interest into the field to yield the number of projects associated with that disease. The user then activated the Active Projects feature and selected 2019 and 2020 in the Fiscal Year dropdown. RePORTER then generated a graph of the study sections that had reviewed the most grants for that autoimmune disease. The study sections appearing in the graph, and the number of grants each study section reviewed, constitute the data included in Table 6-8.

<sup>17</sup> Data of this nature change in the RePORTER system over time. For its analysis, the committee selected active projects; as projects conclude, they are no longer generated when the “active” option is chosen.

**TABLE 6-10** Chartered Study Sections That Reviewed Funded Grants (FY 2019–2020) According to Select Autoimmune Diseases\*

	Sjögren's Disease	SLE	APS	RA	Psoriasis	IBD	Celiac Disease	PBC	MS	T1D	Crohn's Disease	Hashimoto's Thyroiditis
Gastrointestinal Mucosal Pathobiology						25	1				13	
Hypersensitivity, Autoimmune and Immune-Mediated Diseases		11		6					6	9		
Arthritis, Connective Tissue and Skin		8		6	3							
Oral, Dental and Craniofacial Science	7			4							2	
Cellular and Molecular Immunology B		3			1	4			3			
Clinical Neuroimmunology and Brain Tumor									11			
Innate Immunity and Inflammation		4				3					3	
Cellular and Molecular Biology of Glia									8			

*continued*

**TABLE 6-10** Continued

	Sjögren's Disease	SLE	APS	RA	Psoriasis	IBD	Celiac Disease	PBC	MS	T1D	Crohn's Disease	Hashimoto's Thyroiditis
Clinical and Integrative Diabetes and Obesity										8		
Cellular Aspects of Diabetes and Obesity										6		
Hepatobiliary Pathophysiology								6				
Skeletal Biology and Developmental Disease				3								
Diseases and Pathology of the Visual System	2											
Molecular and Cellular Endocrinology												2
Atherosclerosis and Inflammation of the Cardiovascular System			1									
Cellular Signaling and Regulatory Systems							1					

	Sjögren's Disease	SLE	APS	RA	Psoriasis	IBD	Celiac Disease	PBC	MS	T1D	Crohn's Disease	Hashimoto's Thyroiditis
Genetics of Health and Disease	1											
Hemostasis, Thrombosis and Blood Transfusion			1									
Immunology and Host Defense					1							
Macromolecular Structure and Function B							1					

\*Table does not reflect all funded grants; it reflects funded grants portrayed in RePORTER-generated graphs that depicted the study sections that reviewed the most grants for the disease-specific searches. Table reflects data available as of October 5, 2021.

NOTE: APS, antiphospholipid syndrome; IBD, inflammatory bowel disease; MS, multiple sclerosis; PBC, primary biliary cholangitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes

SOURCE: NIH, 2021f.

## NIH AUTOIMMUNE DISEASE RESEARCH: INDICATORS OF ACCOMPLISHMENTS

The statement of task directed the committee to include NIH accomplishments in its report. The committee addressed this task by conducting a high-level review of a number of activities and measures that reflect progress in research (clinical trials and patents), and indicators of scientific performance, quality, and influence on the research field (bibliometric indicators). The committee describes the results of its examination below.

### Clinical Trials

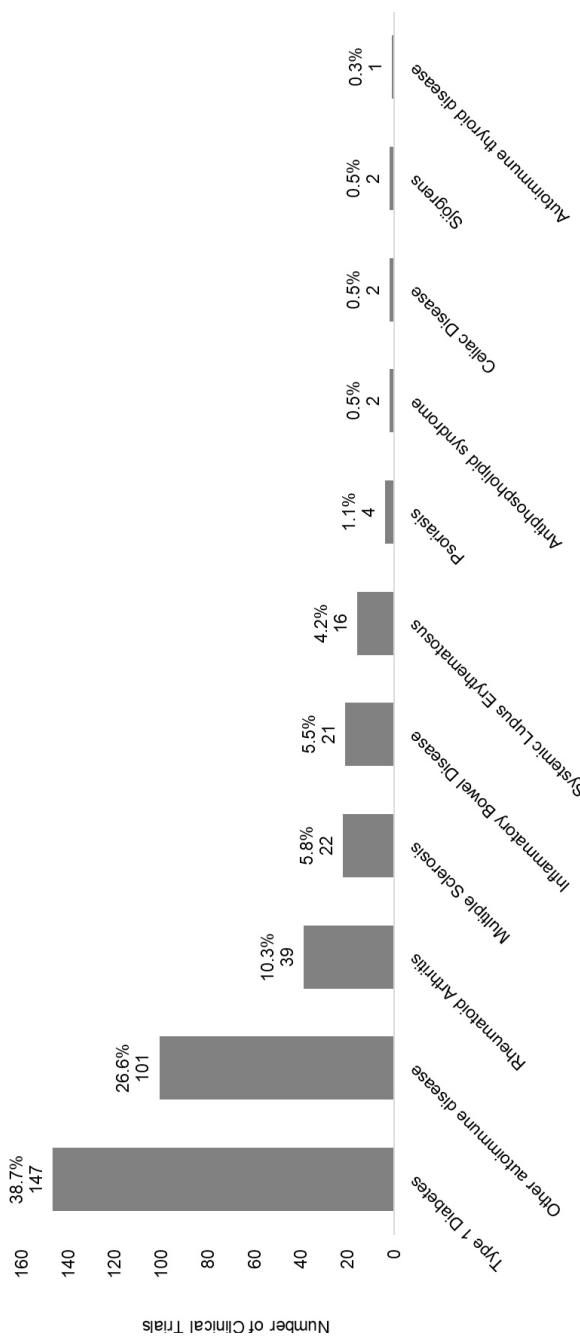
Results of biomedical research on autoimmune disease can yield opportunities to improve the prevention, detection, and treatment of these diseases. Clinical trials, also known as interventional studies, translate basic science knowledge for use in clinical care (NLM, 2021a). Clinical trials focus on developing, testing, and implementing diagnostics and therapeutics across a wide range of diseases and conditions to evaluate the effects of the interventions on safety and health-related outcomes (NLM, 2021a). The committee examined clinical trial activity by autoimmune disease as one measure of research portfolio advancement.

The committee obtained clinical trial data from clinicaltrials.gov<sup>18</sup> and linked clinical trials to the grants associated with the committee's autoimmune diseases of interest. Clinical trials were de-duplicated using their Clinical Trial ID and included based on their relevance to the committee's specific diseases of interest and autoimmune disease as a broader category ("other autoimmune disease"). Ultimately, the committee identified 353 autoimmune disease clinical trials between filing year 2008 and 2020. The "other autoimmune disease" category represents approximately 27 percent of the clinical trials. The remaining 73 percent were associated with one or more autoimmune disease.

Figure 6-26<sup>19</sup> shows the number of clinical trials by disease from filing years 2008–2020. The top five autoimmune disease categories with the most clinical trials over the study period were type 1 diabetes (38.7 percent), other autoimmune disease (26.6 percent), rheumatoid arthritis (10.3 percent), multiple sclerosis (5.8 percent), and IBD (5.5 percent). Each of the remaining autoimmune diseases accounted for less than 5 percent of clinical trials over this period. Clinical trials were fewer for the remaining autoimmune diseases.

<sup>18</sup>Grants with an RCDC code for "Autoimmune Disease" obtained from NIH RePORTER for Fiscal Year 2008 (October 1, 2008–September 30, 2008) through Fiscal Year 2020 (October 1, 2019–September 30, 2020).

<sup>19</sup> See Appendix G for methodology.



**FIGURE 6-26** Clinical trials by autoimmune disease, 2008–2020 (N=353).

NOTE: Percentages in the figure sum to more than 100 percent because clinical trials can be associated with more than one autoimmune disease.

SOURCES: NIH, 2021c, 2021f.

Out of the 353 clinical trials pertaining to autoimmune disease, 20 are phase 4 clinical trials. A phase 4 clinical trial is a “phase of research to describe clinical trials occurring after the Food and Drug Administration (FDA) has approved a drug for marketing. They include postmarket requirement and commitment studies that are required of or agreed to by the study sponsor, and gather additional information about a drug’s safety, efficacy, or optimal use”(NLM, 2021a). Table 6-11 lists select phase 4 clinical trials.

### Publications

The research community often looks to publication citations and other bibliometric measures as indicators of scientific performance, quality, and influence on a research field. The committee selected a number of these measures to examine the performance of the autoimmune disease research portfolio from 2008–2020. These indicators include the number of publications associated with funded grants, relative citation ratio, and journal impact factor.

The committee conducted a bibliometric analysis of publications in PubMed associated with autoimmune disease-associated grant numbers in an effort to characterize scientific productivity and impact. Figure 6-27<sup>20</sup> shows publications by disease category per year. Of the autoimmune diseases examined, the four diseases associated with the greatest number of publications over the 2008–2020 period were other autoimmune disease

**TABLE 6-11** Phase 4 Clinical Trials, Autoimmune Disease Prevention or Treatment

Official Title	Condition or Disease	Primary Purpose
RHYTHM (RHeumatoid Arthritis studY of THe Myocardium): How Rheumatoid Arthritis (RA) and Tumor Necrosis Factor (TNF) Inhibitors Affect the Myocardial Structure and Function.	Rheumatoid Arthritis	Prevention
New Onset Type 1 Diabetes: Role of Exenatide	Type 1 Diabetes	Treatment
Multicenter Open-label Study Evaluating the Safety and Efficacy of Standardized Initial Therapy Using Either Mesalamine or Corticosteroids Then Mesalamine to Treat Children and Adolescents With Newly Diagnosed Ulcerative Colitis.	Inflammatory Bowel Disease (Ulcerative Colitis)	Treatment

SOURCES: NIH, 2018, 2020b, 2021c, 2021e.

<sup>20</sup> See Appendix G for methodology.

(27.7 percent), IBD (22.5 percent), type 1 diabetes (18.2 percent), and multiple sclerosis (16.1 percent).

Figure 6-28<sup>21</sup> shows the trends in autoimmune disease publications. Between publication year 2008 and 2020, other autoimmune disease publications (light purple) generally trended upward and had the most publications overall with an average of 3,398 per year. Publications associated with IBD (yellow) had the greatest number of publications among the committee's diseases of interest but appear to have peaked in 2014. Publications associated with type 1 diabetes (black), multiple sclerosis (dark purple), and SLE (light blue) have also trended downward.

The Relative Citation Ratio (RCR) is a metric developed within the NIH Office of Portfolio Analysis (OPA). RCR "represents the field- and time-normalized citation rate" to the expected citation rate based upon the article's co-citation network of NIH-funded publications (Hutchins et al., 2016; NIH, 2021d). A publication with an RCR of 1 means that it has the same influence as the average article. The RCR metric can be used to determine the allocation of research funding and the extent to which NIH awardees "maintain high or low levels of influence on their respective fields of research" (Aksnes et al., 2019; Hutchins et al., 2016). RCR is often used under the assumption that citations are a proxy for quality; however, articles can be cited for a variety of reasons and RCR does not take the specific context of a citation into account (NIH Library, 2020). This counters the argument that RCR, alone, is a measure of quality.

Table 6-12<sup>22</sup> shows the publications with RCRs by disease. IBD publications had the highest average RCR of 3.029 and are therefore three times as influential as the average article according to this metric. Although PBC publications had the lowest average RCR of 1.894, they are still approximately twice as influential as the average article.

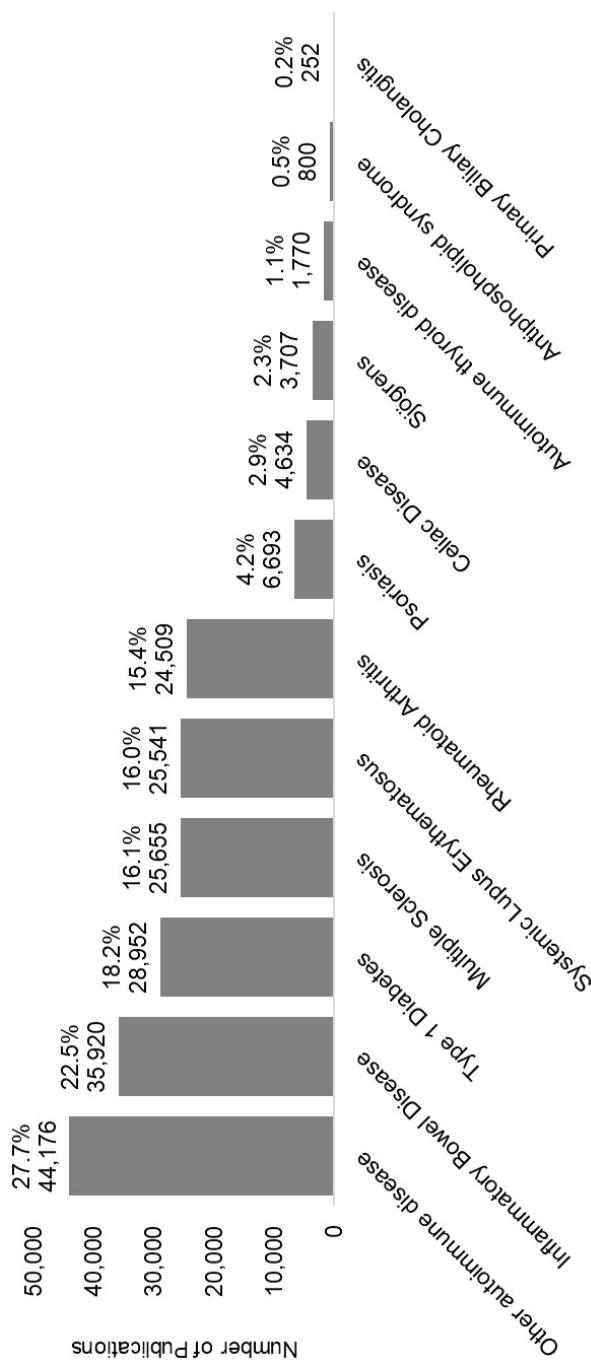
Journal impact factor (JIF) is "a measure of the frequency with which the average article in a journal has been cited in a particular year and it is used to measure the importance or rank of a journal by calculating the times its articles are cited" (University of Illinois Chicago Library, 2016). The scientific impact of an individual article is unrelated to the impact factor of a journal (The University of Texas MD Anderson Cancer Center, 2021), and JIF is a measure of journal quality exclusively. In the context of evaluating NIH's autoimmune disease portfolio, the committee focused on publications resulting from NIH-funded autoimmune disease research and the quality of the journals in which they are published.

Figure 6-29<sup>23</sup> shows average JIF for the 10 journals with the highest JIF for all projects. Of the 159,416 autoimmune disease-related publications,

<sup>21</sup> See Appendix G for methodology.

<sup>22</sup> See Appendix G for methodology.

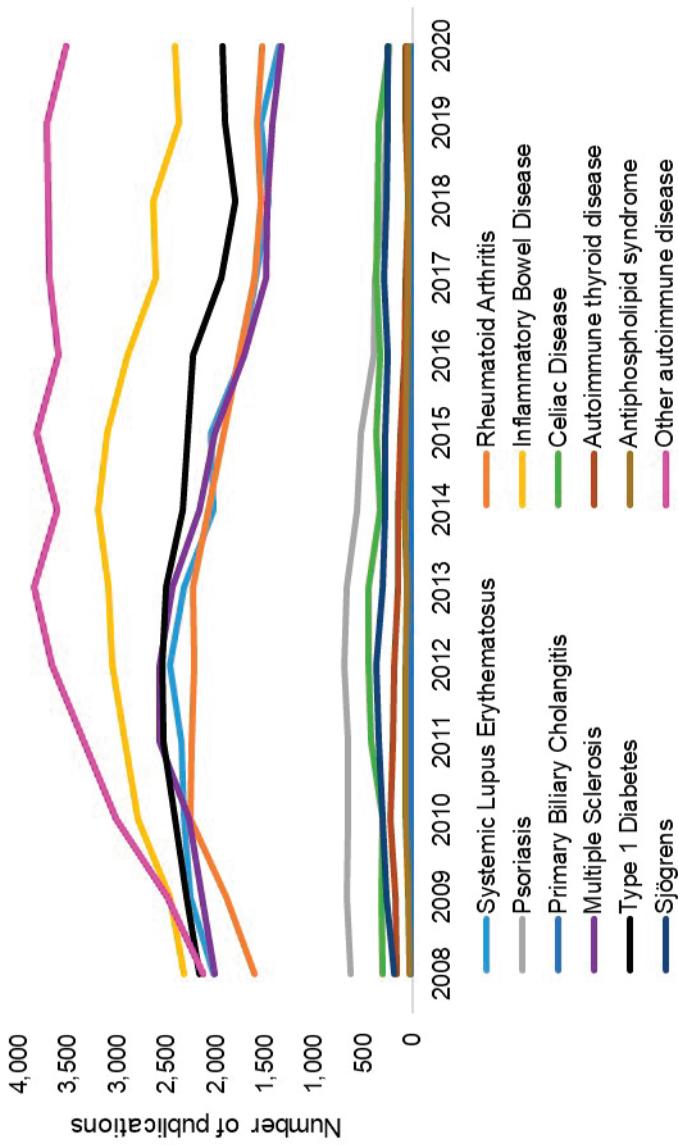
<sup>23</sup> See Appendix G for methodology.



**FIGURE 6-27** Publications by autoimmune disease, 2008–2020 (N=159,416).

NOTE: Percentages in the figure sum to more than 100 percent because publications can be associated with more than one autoimmune disease.

SOURCES: Clarivate, 2021; NIH, 2015, 2021f; NLM, 2021b.



**FIGURE 6-28** Number of autoimmune disease publications by disease and year, 2008–2020 (N=159,416).  
 SOURCES: Clarivate, 2021; NIH, 2015, 2021f; NLM, 2021b.

**TABLE 6-12** Publications with RCRs by Autoimmune Disease, 2008–2020 (N=152,286)

Autoimmune Disease	Publication Count with RCR	Mean	Median	Range
Inflammatory bowel disease	34,540 (22.7%)	3.029	1.366	0 to 634.738
Other autoimmune disease	41,996 (27.6%)	2.445	1.281	0 to 275.191
Celiac disease	4,493 (3%)	2.387	1.274	0 to 61.164
Rheumatoid arthritis	23,497 (15.5%)	2.379	1.281	0 to 211.184
Autoimmune thyroid disease	1,724 (1.2%)	2.365	1.200	0 to 91.059
Psoriasis	6,539 (4.3%)	2.360	1.278	0 to 213.283
Multiple sclerosis	24,841 (16.4%)	2.349	1.228	0 to 216.311
Type 1 diabetes	27,691 (18.2%)	2.207	1.186	0 to 621.789
Systemic lupus erythematosus	24,671 (16.3%)	2.175	1.205	0 to 621.789
Antiphospholipid syndrome	772 (0.6%)	2.164	1.269	0 to 38.859
Sjögren's disease	3,523 (2.4%)	2.093	1.233	0 to 43.621
Primary biliary cholangitis	247 (0.2%)	1.894	1.183	0 to 31.923

NOTES: Publications must be 2–3 years old in order to have enough citations to calculate an RCR. RCR, Relative Citation Ratio.

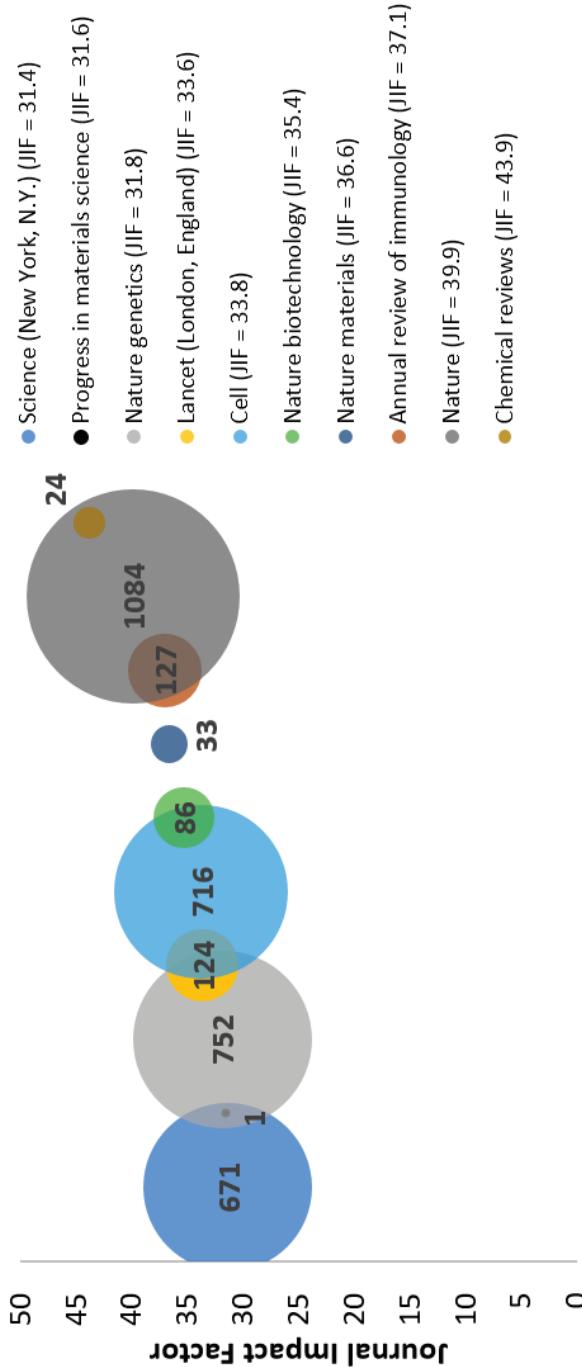
SOURCES: Clarivate, 2021; NIH, 2015, 2021f; NLM, 2021b.

63 percent (101,199 of 159,416) had JIF data. The size of the bubble represents the number of publications in the journal, while the location of the bubble on the y-axis shows the JIF relative to each other. Although *Nature* (dark gray) published the most articles between 2008 and 2020, *Chemical Reviews* (brown) has the highest JIF (43.9). In most fields, the impact factor of 10 or greater is considered an excellent score while 3 is flagged as good and the average score is less than 1 (*SCI Journal*, 2021).

## Patents

A patent grants a property right to the inventor and prohibits others from offering, selling, or importing that invention (USPTO, 2018). Patents granted as a result of NIH-funded autoimmune disease research aim to encourage and protect biomedical innovation and may serve as a proxy for knowledge generation and translational value in the field (Kalutkie-wicz and Ehman, 2014). The committee examined patents and patent applications by autoimmune diseases.

The committee obtained patent data linked to the grants associated with the committee's autoimmune disease of interest from the United



**FIGURE 6-29** Average JIF for the 10 journals with the highest JIF for all autoimmune disease publications, 2008-2020.  
 NOTES: Because of the vast differences in the size of citation pools for general journals (large citation pools) versus very specialized journals (smaller citation pools), caution should be taken when comparing general and specialized journals without normalization. JIF, Journal Impact Factor.

SOURCES: Clarivate, 2021; NIH, 2015, 2021f; NLM, 2021b.

States Patent and Trademark Office (USPTO) at uspto.gov. A total of 4,113 patent applications and patents were associated with NIH grants funding research in autoimmune diseases, of which 60 percent (2,470 of 4,113) were patent applications and 40 percent (1,643 of 4,113) were granted applications (patents). All were included in the analysis. A total of 30 percent of the patents and patent applications were associated with only one disease category. The remaining 70 percent were associated with more than one disease category.

Figure 6-30<sup>24</sup> shows the number of patent applications by disease for filing years 2008–2020. The top three autoimmune disease categories with the most patent applications were other autoimmune disease (30.3 percent), multiple sclerosis (22.8 percent), and IBD (19.8 percent). Fewer patent applications were filed for the remaining autoimmune diseases.

Figure 6-31<sup>25</sup> shows the granted patents by disease for filing years 2008–2020. The top three disease categories with the most patents were other autoimmune disease (29.1 percent), multiple sclerosis (22.7 percent), and IBD (18.4 percent).

The ultimate outcome of clinical and biomedical research is an observable impact on the health and wellbeing of individuals. This downstream effect is a result of fundamental scientific knowledge “applied to develop actionable interventions that are implemented to enhance health, lengthen life, and reduce illness and disability” (NIH, 2014). Publications disseminated throughout the scientific community often report the outcomes of clinical and biomedical research, and the number of publications resulting from autoimmune disease-related research is astounding, as seen by the thousands of relevant autoimmune-related publications produced between 2008 and 2020.

The committee was unable to perform a comprehensive assessment of research accomplishments and successes and therefore was unable to assess clinical and biomedical achievements as a measure of knowledge in the field beyond quantifying publications, patents, and clinical trials. Another way to assess achievements is to determine how research translates into clinical care and treatment of individuals, but this too is an immense undertaking. Instead, the committee provides a number of illustrative research findings associated with the research portfolio that have the potential to improve the health and healthcare of individuals living with autoimmune diseases in Table 6-13.<sup>26</sup>

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<sup>24</sup> See Appendix G for methodology.

<sup>25</sup> See Appendix G for methodology.

<sup>26</sup> Autoimmune Disease Research Highlights were collected from NIH biennial and triennial reports to Congress, and NIH websites.

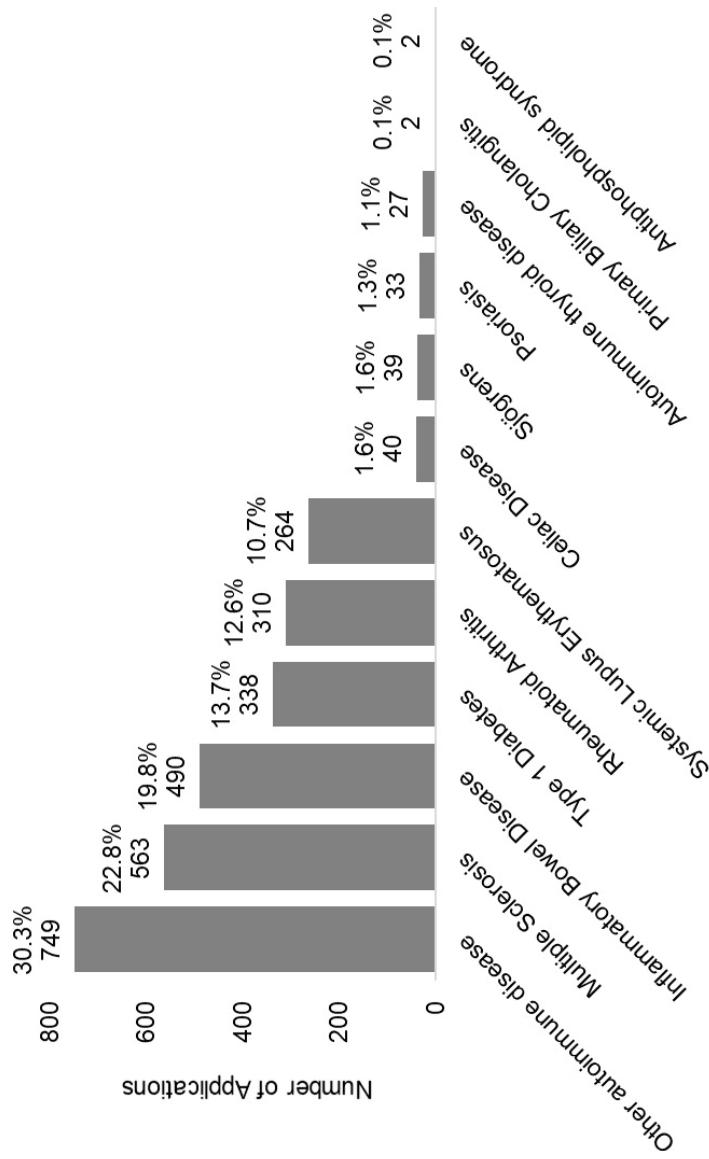
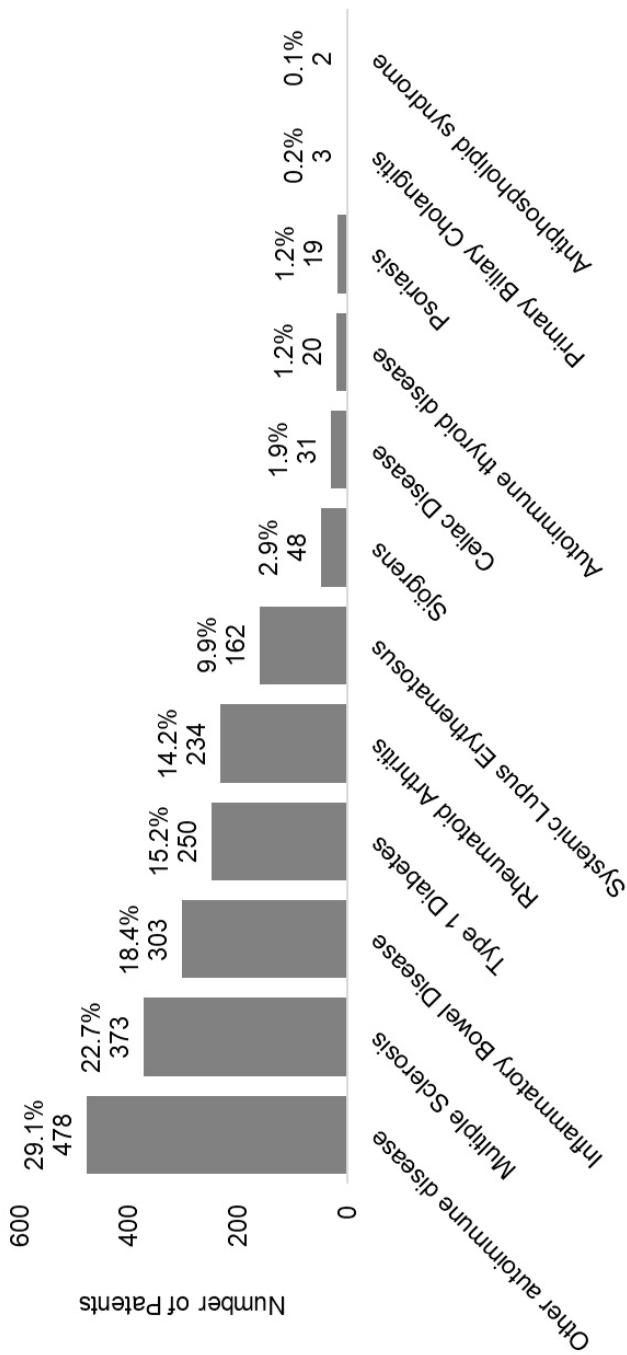


FIGURE 6-30 Patent applications by disease, 2008–2020 (N=2,470).

NOTE: Percentages in the figure sum to more than 100 percent because patients can be associated with more than one autoimmune disease.

SOURCES: NIH, 2021f; USPTO, 2018.



**FIGURE 6-31** Patents by disease, 2008–2020 (N=1,643).

NOTE: Percentages in the figure sum to more than 100 percent because patients can be associated with more than one autoimmune disease.

SOURCES: NIH, 2021f; USPTO, 2018.

**TABLE 6-13** Autoimmune Disease Research Highlights

Finding	Description
	Sjögren's disease
Research on Interferons Could Identify Individuals with Sjögren's Disease Most Likely to Respond to Treatment	Investigators have found that a high level of interferons (IFNs, that is, proteins produced in the inflammatory response to infections) to be associated with a more severe form of Sjögren's disease for more than 50 percent of patients studied. This finding paves the way for "precision-based medicine," a customized treatment approach which tailors health care based on a person's genes to those patients most likely to respond to certain therapies, such as anti-IFN treatments. In addition, it could improve the selection of for clinical trials. "Stratification" of candidates is particularly important given differences among patients with Sjögren's disease. Such heterogeneity complicates disease classification, assignment of disease mechanism and selection of therapy (Hall et al., 2015).
Immunomonitoring Can Predict Complications of Lupus Pregnancies	Unique "immune signatures" can identify pregnant patients with SLE who could suffer such complications as preeclampsia, high blood pressure and damage to organ systems such as the liver and kidneys, which endanger the mother, and death of a fetus as well as issues with fetal growth and preterm delivery. Such outcomes affect over one-fifth of SLE pregnancies. Researchers concluded that immune signatures, more accurate than clinical assessments, can predict the development of preeclampsia and adverse outcomes for the fetus. Their findings provide a framework for developing treatments to reduce morbidity and mortality complications in pregnant patients with lupus (Hong et al., 2019).

*continued*

**TABLE 6-13** Continued

Multiple sclerosis	
Stem Cell Transplants Leads to Positive Outcomes for Multiple Sclerosis Patients	Research which transplanted stem cells for treatment of MS led to positive outcomes for patients with the relapsing form of MS. Almost half of those in the study remained free from neurological progression of the disease five years after the transplant. Better outcomes such as improvement in bone marrow and “resetting” of the immune system are associated with such factors for patients as younger age, fewer prior immunotherapies and not having reached high disability levels. For researchers, such results justify a future clinical trial on stem cell transplants for treating MS including an evaluation of safety and efficacy against approved therapies of high efficacy. Another trial could address whether this therapy can reduce the progression of disability in patients with a progressive form of MS that is worsening neurological function from the onset of symptoms without relapses or remissions (Muraro et al., 2017).
Type 1 diabetes	
Early Preventive Treatment Delays Onset of Type 1 Diabetes	Study of treatment with teplizumab found that this immune system-modulating drug delayed the onset of type 1 diabetes in high-risk but nondiabetic relatives of patients with diabetes. The delay of progression to type 1 diabetes is particularly important given that it is the second most common disease of childhood after asthma. At-risk children progress to type 1 diabetes more rapidly than adults. Once this condition develops, children can face such challenges as managing it on a daily basis and those who are not treated face life-threatening complications. Building on this study, next steps include testing the long-term efficacy and safety of teplizumab (Herold et al., 2019).

**TABLE 6-13** Continued

Artificial Pancreas System Controls Diabetes in Children	<p>A clinical trial at four U.S. pediatric centers found that a new artificial pancreas system effectively manages blood glucose in children as young as age six. The artificial pancreas, also known as a “closed-loop control,” is an “all-in-one” diabetes management system which tracks blood glucose levels and automatically delivers insulin when needed. By replacing reliance on fingerstick testing with delivery of insulin by multiple daily injections (or pump controlled by the patient or caregiver), this system can improve the quality of life and disease management for youth (Breton et al., 2020).</p>
Rheumatoid arthritis	
Lung Diseases Such as Asthma Increase the Risk of Rheumatoid Arthritis	<p>Research has found that women with lung diseases such as asthma or chronic obstructive pulmonary disease (COPD) have an increased risk of developing rheumatoid arthritis (RA). This is independent of smoking which is a strong environmental risk factor for the development of RA. Early detection of RA through monitoring of such patients could mean lowering the risk of long-term adverse consequences in the future (Ford et al., 2020).</p>
Inflammatory bowel disease	
Discovery of Biomarker Holds Potential for Improved Treatment of Ulcerative Colitis in Children	<p>Because irritable bowel disease makes it difficult for food nutrients to be absorbed, growth in children who have ulcerative colitis (a type of IBD limited to the colon) can be stunted due to malnutrition. The PROTECT Study (Predicting Response to Standardized Pediatric Colitis Therapy) has examined responses to treatment by children newly diagnosed with ulcerative colitis. This study determined that the presence in the blood of a biomarker called pANCA (Perinuclear anti-neutrophil cytoplasmic antibody) is associated with more extensive resistance to therapy for this disease. These are antibodies to a type of white blood cell called neutrophil. The identification of this biomarker indicates its potential as a diagnostic tool for planning individual treatments for children with this disease (Spencer et al., 2018).</p>

*continued*

**TABLE 6-13** Continued

<p><b>Identification of Unique Cellular Signatures for Crohn's Disease Patients May Improve Treatment in the Future</b></p>	<p>Clinical benefits of certain treatments which can block the inflammatory response in Crohn's disease have not worked for all patients and drug trials for patients with IBD have had limited success in recent decades. As a result, radical measures such as surgical removal of affected areas in the small intestine may be necessary.</p> <p>Recent research identifies a distinctive combination of cells in those people with Crohn's disease who do not respond to "anti-TNF" drugs. (TNF or tumor necrosis factor refers to an inflammation causing protein in the body.) Analysis of how the cells communicate with each other showed that this particular cellular combination does not rely solely upon the tumor necrosis factor to maintain gut inflammation. This may explain why TNF-blocking drugs are ineffective. This analysis also identifies several other molecular targets for other potential therapies that, if used in combination with TNF-blocking drugs might be able to prevent inflammation in people with Crohn's disease who do not respond to anti-TNF medications alone. Such enhanced understanding of differences in cellular makeup can shed light on the nature of Crohn's disease and help predict which treatments might be effective (Martin et al., 2019).</p>
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## SUMMARY

In reviewing NIH's research portfolio on autoimmune diseases, the committee employed a general framework that considered the inputs (spending), activities (research conducted), and outputs (clinical trials, patents, and other indicators) of NIH's investment in autoimmune disease research. Spending on autoimmune diseases as a percentage of overall NIH obligations has remained at only 2.6 percent between 2013 and 2020. This is in marked contrast to increases seen in overall NIH obligations during the same time period. In addition, the distribution of this funding for autoimmune diseases indicates that certain ICs dominate overall spending on research and training and the types of research activities funded. NIH may need to reconsider the current strong focus on investigator-initiated research in order to target areas of high priority and effectively address the long-term, complex, and heterogeneous nature of autoimmune diseases.

Regarding the activities conducted under funded autoimmune disease research grants, the multiple methods the committee used yielded

useful information at different levels of specificity. However, metrics are not available for evaluating the overall research portfolio for autoimmune diseases.

The outputs of NIH's investment in autoimmune disease research can be measured in a variety of ways, including clinical trials (the translation of research knowledge into interventions), publications, and the number of patents associated with autoimmune disease research grants (an important indicator of innovation). There is a greater percentage of clinical trials from filing years 2008–2020 for such autoimmune diseases as type 1 diabetes, SLE, IBD, and rheumatoid arthritis, with a much smaller percentage seen for other autoimmune diseases. In general, the knowledge associated with existing research grants has been successfully disseminated to the research community through publications in well-regarded scientific journals. In terms of patent applications, filings occur primarily for some autoimmune diseases with far fewer filings for others. In general, findings related to research outputs suggest the need for a nuanced and in-depth examination of why progress via clinical trials and patent filings does not seem to have been made for certain autoimmune diseases.

Given the findings of Chapter 6, the committee concludes that the absence of an overarching strategic plan with concrete metrics makes it difficult to assess the distribution of funding by IC or disease. The committee also concludes that the relatively small percentage of NIH funding devoted to autoimmune disease research and how it is distributed could be a significant factor in hampering scientific progress on diseases that affect more than 23 million people.

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## Opportunities and Options for Enhancing Autoimmune Disease Research at NIH

In this chapter the committee reviews its response to the statement of task and highlights observations that form the basis for its consideration of potential opportunities and options for enhancing autoimmune disease research at the National Institutes of Health (NIH).

Chapters 2 and 3 provide ample evidence that autoimmune diseases exact a difficult toll and inflict severe burdens on the U.S. population, with consequences that compromise quality of life for those afflicted. Many autoimmune diseases affect women predominantly, and the incidence and prevalence of these diseases appears to be rising in certain groups, such as children and adolescents in the case of two of the most common autoimmune diseases, namely inflammatory bowel disease and type 1 diabetes. The burden of some autoimmune diseases is higher among specific minority racial and ethnic populations, which also contributes to the importance of enhancing research in these areas.

As described in Chapter 2, the committee realized that it faced a daunting task given definitional issues and the lack of basic data. It found that autoimmunity and autoimmune disease are evolving and dynamic areas in which definitions of autoimmune disease and the number of diseases identified as such continue to evolve and change. Recent scientific advances have blurred the definition of autoimmune disease, there is no consensus on the best terms or methods to conceptualize autoimmune disease to meet the differing views and purposes of basic and clinical research, and there is no consensus regarding the number of

autoimmune diseases. The committee could not identify a concerted NIH effort addressing these issues.

A second challenge the committee faced was the lack of basic epidemiologic data on the incidence and prevalence of autoimmune diseases. There is no mandatory reporting system or national registry for autoimmune diseases in the United States. Existing incidence and prevalence data often come from other countries that have health care systems covering the entire population. In the United States, data are incomplete and often outdated, which can limit the ability to assess whether progress has been or is being made in reducing the burden of these diseases. The committee could not identify a concerted NIH effort to improve the availability of population-level data on autoimmune disease.

The committee's examination of 11 diseases illustrating the spectrum of autoimmune diseases emphasizes the variation in what is known and unknown about each disease. For example, gaps exist in the epidemiology of most autoimmune diseases; basic molecular mechanisms are not clearly elucidated for many autoimmune diseases; important questions remain regarding risk factors and etiology for most autoimmune diseases; and diagnostic tools are limited or lacking for some autoimmune diseases. Further, there is tremendous variation in how diseases present, progress, and evolve, which complicates diagnosis and treatment. Autoimmune diseases can be treated; treatment is aimed at reducing symptoms and improving function and quality of life, but for some autoimmune diseases, information is lacking on how best to target therapies to individuals. Finally, the committee found limited information on the social and economic impact of autoimmune diseases on affected individuals and their families.

Chapter 4 describes commonalities among autoimmune diseases. These commonalities suggest common immune pathways among some diseases or groups of diseases, including the role of genetics, biologic sex, and environmental exposures. Advances in technology allow researchers to capture, manipulate, and optimize enormous quantities of data from basic and clinical research, which they can in turn use to form hypotheses. The committee believes these commonalities regarding shared gene and immune pathways may provide additional and significant insights that can further the development of treatments and therapies that could benefit patients suffering with these diseases. For this area of inquiry to advance, a multidisciplinary approach will be needed that draws upon the expertise of researchers from across NIH.

Chapter 5 describes the NIH research grant process and coordination of autoimmune disease research. The committee found that the Autoimmune Disease Coordinating Committee (ADCC) has no dedicated funding or staff and functions as a convener of Institutes and Centers (ICs)

and external partners. It was unable to assess the extent to which ADCC activities have expanded, renewed the focus on, or provided enhanced coordination of autoimmune disease research.

The committee reviewed the NIH research portfolio on autoimmune disease with an appreciation of the research gaps highlighted in Chapters 2 through 4. The general framework for this review included, to the extent possible, reviewing a set of inputs, activities, and outputs. Among the inputs reviewed were NIH spending for autoimmune disease research grants and procedures for awarding grants, as well a review of individual IC missions and strategic plans. The committee found that there is no central repository for information on autoimmune disease research activity undertaken by ICs across NIH. Committee members reviewed IC strategic plans, websites, and other information to obtain insights into the autoimmune disease research priorities of the ICs reviewed and to identify which autoimmune diseases might be relevant to their missions. The committee notes that the lack of a central repository for autoimmune disease research at NIH hampers the ability of individuals in and outside of NIH, and in and outside of the research enterprise, to readily access this information and consequently limits transparency and communication with the public and other stakeholders.

The committee found that NIH spending on autoimmune disease research has remained constant at about 2.8 percent of total spending between 2008 and 2020 while there are indications that some autoimmune diseases are on the rise and that many individuals are living with autoimmune disease. If resources increase for autoimmune disease research, a strategy for prioritizing, leveraging, and assuring that funds are invested in the areas of highest scientific priority would be essential. Similarly, if budgets remain constrained, the need for strategic prioritization is even greater. The committee did not find evidence of current crosscutting autoimmune disease research budgeting, planning, or prioritization.

The committee next reviewed the focus of the funded autoimmune disease research grants as the statement of task requested. It used three different approaches, which indicated significant variation in the focus of research grants. This is consistent with the fact that 73 percent of autoimmune disease research grants are investigator initiated. The committee notes that in the NIH Research, Condition, and Disease Category (RCDC) analysis of co-occurring RCDC spending categories, autoimmune disease relevant themes such as minority health, pain research, and co-occurring complications, conditions, or diseases (e.g., chronic pain, cancer, cardiovascular disease, depression, eye disease and disorders) co-occurred in less than 10 percent of autoimmune disease grants. Spending category themes related to burden of illness, caregiving, and health services co-occurred in less than 2 percent of grants.

The analysis of the focus of autoimmune disease grants using different methods provided limited information. The committee had no basis upon which to determine whether (1) the funded grants represent the most promising, innovative, or impactful autoimmune disease research areas; (2) dollars are appropriately distributed by research topic area (e.g., crosscutting research, basic science, clinical science, specific autoimmune diseases); and (3) fellowships, research career, and training program grants appropriately support the development of a multidisciplinary and diverse autoimmune disease research workforce. A crosscutting strategic plan to guide current research activities with details on specific goals, objectives, timelines, and milestones would have provided an important reference point to guide the assessment of the current portfolio. Developed 20 years ago, the last autoimmune disease research plan lacked such details.

Shared immune pathways among autoimmune diseases noted earlier suggest opportunities for cross-IC collaboration and coordination of research activities. The committee's analysis of IC collaborations on joint research funding opportunities from 2008 to 2020 indicates an average of four or fewer IC collaborations during the period. Based on this finding, the committee raises the question as to whether ICs can do more to collaboratively leverage cross-NIH expertise and resources to advance autoimmune disease research activities.

Finally, the committee attempted to assess the output or accomplishments associated with funded research on autoimmune disease. This effort included a high-level examination of clinical trial activity representing the translation of research knowledge into interventions that influence health-related biomedical or behavioral outcomes. Clinical trials have centered on certain autoimmune diseases but not for other diseases that receive limited funding, perhaps indicating that research has not yet progressed to this stage. The committee also considered a number of bibliometric indicators: number of publications; the relative citation ratio, a research influence indicator; and the journal impact factor, which indicates the quality of the journal that published the article. A final task involved identification of the number of patents associated with autoimmune disease research grants as an indicator of innovation and the translational value of autoimmune disease research activities.

The committee's review of the NIH autoimmune disease research portfolio confirms that much extraordinary work related to autoimmune disease has been undertaken and likely will continue. The committee was struck by the number of research grants (8,470) it identified as related to autoimmune disease during the fiscal year 2008–2020 period and the extent to which knowledge associated with these grants has been disseminated to the research community through publications, translated into

potential interventions, and driven innovation as indicated by approved patents.

In sum, the committee found that autoimmune diseases impact the lives of millions of Americans. Autoimmune diseases are complex and share commonalities that would benefit from a coordinated, multidisciplinary research approach to better understand basic mechanisms, etiology and risk factors, and to support the development of interventions to mitigate the impact of autoimmune diseases and associated co-morbidities and complications across the lifespan. Current NIH autoimmune disease research efforts are guided by a dated research plan, and efforts to coordinate autoimmune disease research are minimal. Information on autoimmune disease research activities is difficult to identify across ICs, and this hinders transparency and communication with internal and external stakeholders. Finally, the committee found there is no central entity with capabilities to improve communication, management, priority setting, and accountability for autoimmune disease research. The committee concludes that these findings can be usefully framed as future opportunities for enhancing the research enterprise for autoimmune diseases.

## PLANNING, COLLABORATION, AND INNOVATION

The committee offers a framework of five essential elements to enhance the rapid advancement and improvement in autoimmune disease research—(1) strategic research planning to set priorities, (2) an emphasis on coordinating across NIH ICs and enhancing collaborative research given the crosscutting nature of autoimmune disease, (3) an orientation toward innovation, (4) a focus on evaluating the autoimmune disease research portfolio to determine progress made across NIH, and (5) resources to support planning, collaboration, and innovation. These critical elements, which can be viewed as complementary, are recognized by research literature, NIH in its overall strategic plan, and the findings of this study. While the committee recognizes that the diffuse and investigator-initiated nature of NIH research, and of autoimmune disease research in particular, has many well-described and accepted advantages, this approach does not optimally promote these five elements given barriers identified by the committee. While several individual ICs address autoimmune diseases in strategic plans and may reference elements such as collaboration and evaluation, others do not.

Beyond individual ICs, an overarching barrier is the absence of an overall strategic research plan for NIH work on autoimmune disease that would prioritize coordination of and collaboration in research, act as an impetus to increased innovation, and include attention to evaluation. The ADCC has not developed a strategic research plan in this area since 2002,

and this plan did not have an evaluative component given the absence of milestones or metrics. In contrast, the *National Plan to Address Alzheimer's Disease*, another area of crosscutting attention by various ICs, lays out guiding principles, concrete goals as building blocks for transformation that reference the importance of tracking progress, and related strategies that identify lead agencies and potential research partners in the public and private sectors (AIM, 2021; HHS, 2020).

In the area of autoimmune disease research, a relatively independent, structured, and ongoing examination of the research conducted can identify where gaps and opportunities lie. This analysis can then inform planning for how to address those gaps and opportunities most successfully, an effort that would also benefit from a detailed but not prescriptive strategic plan. Currently, neither a rigorous evaluation nor planning for autoimmune disease research across NIH occurs in an overarching, sustained, and resourced fashion.

While the ADCC was tasked to coordinate autoimmune disease research, the committee determined that it currently functions primarily as a convener of ICs and external partners. While meeting participants share information and may coordinate their activities on autoimmune disease research, the ADCC does not have central responsibility and accountability for driving activities and does not have the funding to spur targeted research by ICs.

During the course of this review, the committee identified an opportunity not only for filling gaps that may fall between the work of diverse ICs, but also, as discussed in Chapter 4, capturing and leveraging an understanding of the crosscutting nature of autoimmune diseases, including their underlying common disease mechanisms, risk factors, and commonalities such as coexisting illnesses. The committee believes that emerging and evolving science now makes those connections more achievable than ever before. Such information would doubtless serve as building blocks for and would accelerate innovative progress toward prevention, treatment, and cure.

Some of this work can advance without the infusion of major new resources. However the committee believes that any centralized entity, to be effective, will require new resources, and that a broader and better research enterprise on autoimmune disease has a greater potential to bring relief to patients and their families.

The committee considered five options for enhancing autoimmune disease research and resulting outcomes: increased funding, two options for coordinating research, establishing a national strategic plan, establishing a new institute, and creating a special office for autoimmune disease research. The committee recognizes that no one option will transform the autoimmune disease research enterprise, and that each option involves

tradeoffs. Table 7-1 provides the committee's description of each option, noting advantages and disadvantages for each and offering a high-level assessment of cost and political feasibility. As discussed below, the committee found that the best option for addressing these challenges and opportunities would be creating an office of autoimmune disease in the Office of the Director (OD) that is funded appropriately. Such an office would be positioned to respond to the committee's concerns by:

- Facilitating cross-NIH multidisciplinary collaboration and stimulating innovation around autoimmune disease research;
- Engaging in priority setting, strategic planning, and implementation;
- Budgeting for and allocating available autoimmune disease research funds in alignment with the strategic plan;
- Managing and evaluating autoimmune disease research efforts;
- Communicating with key stakeholders; and
- Providing visible leadership on autoimmune disease research.

### **Option 1: Increased Funding for Autoimmune Disease Research**

Given the flat line of research spending levels over the past 12 years, the committee believes that increased funding will be an indispensable component of any effort to enhance autoimmune disease research opportunities, and thus it lists that option first. Options for use of increased funding include directing funding to certain ICs, such as those whose mission is more directly related to autoimmune disease issues of concern (e.g., National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, and National Institute of Arthritis and Musculoskeletal and Skin Diseases) or increasing funding to ICs that are highly relevant but less well funded (e.g., National Institute of Environmental Health Sciences). ICs with smaller total budgets would have more funding to drive and solicit specific research on autoimmune disease and to bring more dollars and expertise to the table to collaborate meaningfully. As a result, more and potentially better collaborations might occur.

The design of increased funding can include such options as a common fund or direction to certain focused activities. Funding for an "autoimmune disease research common fund" could specifically support more crosscutting research activities that could foster collaboration among ICs. More "risky" or expensive but high-payoff research collaborations could be undertaken. One approach would be to model such a fund after the NIH Common Fund, which makes funds available to address high-priority emerging scientific opportunities and pressing challenges

**TABLE 7-1** Options for Enhancing NIH Autoimmune Disease Research

<b>Option 1. Increased Funding for Autoimmune Disease Research</b>	
Funding may include:	<ul style="list-style-type: none"> <li>Increased funding to certain ICs</li> <li>Increased funding for crosscutting activities (autoimmune disease research common fund)</li> <li>Increased funding for certain focused activities</li> </ul>
Pros: Potential Benefits and Advantages	<ul style="list-style-type: none"> <li>Opportunity for accelerated discovery.</li> <li>Specific ICs, particularly those that are highly relevant but less well-funded, would have more funding to solicit specific research on autoimmune disease and to "bring dollars and expertise to the table" to collaborate meaningfully. Thus more and better collaborations might occur.</li> <li>More "risky" or expensive but high-payoff research collaborations could be undertaken.</li> <li>Increased funding for specific topics of research or workforce development.</li> <li>Relatively low administrative burden since it would leverage mechanisms already in place.</li> </ul>
Cons: Potential Concerns and Disadvantages	<ul style="list-style-type: none"> <li>Funding increases are uncertain/unpredictable, making planning difficult.</li> <li>Unhelpful competition for limited new resources among ICs—and among autoimmune diseases research areas.</li> <li>Without major new funding, new investments in one area may be offset by cuts in another.</li> <li>There may be opposition to earmarking funding for autoimmune disease research.</li> <li>Funding may not address issues of coordination, prioritization, or workforce development.</li> </ul>
Costs	<ul style="list-style-type: none"> <li>Variable but could be high</li> </ul>
Feasibility	<ul style="list-style-type: none"> <li>Contingent on internal NIH and external advocacy and substantial congressional support.</li> </ul>
<b>Option 2. Enhanced Coordination Options</b>	
<b>2a. Revitalize the ADCC</b>	
Pros: Potential Benefits and Advantages	<ul style="list-style-type: none"> <li>Would not require creation of a new entity.</li> <li>Possibility of drawing on past experience with 2002 Autoimmune Disease Strategic Research Plan in developing a new strategic plan.</li> </ul>
Cons: Potential Concerns and Disadvantages	<ul style="list-style-type: none"> <li>Lacks IC neutrality by virtue of its placement within NIAID.</li> <li>ADCC lacks resources to support ICs for credible implementation of strategic plan.</li> <li>Potential reluctance to significantly resource and empower an office that has not had a significant leadership role.</li> <li>ADCC cannot hold ICs accountable for implementing or funding research according to the strategic plan.</li> </ul>

**TABLE 7-1** Continued

Costs	<ul style="list-style-type: none"> <li>• Low</li> </ul>
Feasibility	<ul style="list-style-type: none"> <li>• Easy but would require additional funding to support strategic plan development.</li> </ul>
<b>2b. Establish a Health and Human Services (HHS) Autoimmune Disease Coordinating Committee</b>	
Pros: Potential Benefits and Advantages	<ul style="list-style-type: none"> <li>• Would raise the visibility of autoimmune diseases to the cabinet level.</li> <li>• Engages and potentially leverages other HHS agencies, including their expertise, resources, and reach.</li> <li>• Could anticipate and inform issues—such as special populations (racial and ethnic minority populations, women), payment for health care services, regulation of drugs and devices, and public health issues.</li> <li>• Could enhance engagement with non-HHS agencies, e.g., Social Security Administration regarding disability determinations.</li> <li>• Greater accountability.</li> </ul>
Cons: Potential Concerns and Disadvantages	<ul style="list-style-type: none"> <li>• Downside of broad engagement can be greater bureaucracy (including neglect, and/or resistance), high-level products with little depth, slowness, and lack of external support and politicization.</li> <li>• Would require creation of the body and need appropriate resources (staff, funding, authority).</li> </ul>
Costs	<ul style="list-style-type: none"> <li>• Moderate</li> </ul>
Feasibility	<ul style="list-style-type: none"> <li>• Moderate difficulty: some resistance may be inevitable.</li> </ul>
<b>Option 3: Congressionally Mandated National Autoimmune Disease and Autoimmunity Plan</b>	
Pros: Potential Benefits and Advantages	<ul style="list-style-type: none"> <li>• Imprimatur of Congress brings weight, attention, expectation of results, and likely resources to the issue.</li> <li>• Delineated activities and deliverables provide specificity and focus.</li> </ul>
Cons: Potential Concerns and Disadvantages	<ul style="list-style-type: none"> <li>• Focus on a single disease may obscure or inadvertently exclude other conditions.</li> <li>• Absent specificity, accountability for results may be unclear or diffuse.</li> </ul>
Costs	<ul style="list-style-type: none"> <li>• Moderate</li> </ul>
Feasibility	<ul style="list-style-type: none"> <li>• Would require Congressional action.</li> </ul>

*continued*

**TABLE 7-1** Continued

<b>Option 4: Create a New National Institute of Autoimmune Disease and Autoimmunity</b>	
Pros: Potential Benefits and Advantages	<ul style="list-style-type: none"> <li>• Significantly elevates visibility and status of autoimmune disease research within NIH and externally through leadership, infrastructure, and funding.</li> <li>• Provides sustained leadership and focus to autoimmune disease research. Institute Director, staff, and their external advisers are thinking and working full time on solving autoimmune disease challenges through extramural, intramural, training, communication, and outreach activities.</li> <li>• De facto coordinating body that is crosscutting rather than autoimmune disease-specific.</li> <li>• Establishes clear focal point within NIH and externally. Internal and external accountability and transparency for autoimmune disease research may improve.</li> </ul>
Cons: Potential Concerns and Disadvantages	<ul style="list-style-type: none"> <li>• Requires time to conduct review and receive internal and external input on the creation of a new Institute.</li> <li>• Substantial costs to administratively create and sustain; new appropriations would be needed to avoid reducing autoimmune disease activities in other ICs.</li> <li>• Potential resistance from other Institutes.</li> <li>• Weak, underfunded Institute can give the illusion of increased effort and thus can be worse than an admittedly diffused effort in well-established but less focused ICs.</li> </ul>
Costs	<ul style="list-style-type: none"> <li>• High</li> </ul>
Feasibility	<ul style="list-style-type: none"> <li>• Substantial political obstacles can attend the creation of a new Institute.</li> <li>• Requires congressional approval.</li> </ul>
<b>Option 5: Create an Office of Autoimmune Disease/Autoimmunity Research within the Office of the Director of NIH</b>	
<p>Realistically, the impact of such an Office will likely be proportionate to the extent to which it has and controls resources. Thus two options for an Office are described.</p>	
Pros: Potential Benefits and Advantages	<ul style="list-style-type: none"> <li>• Elevates visibility, provides sustained leadership, and establishes a clear focal point for autoimmune disease research within NIH and externally through extramural, intramural, training, and communication and outreach activities.</li> <li>• De facto coordinating body that is crosscutting rather than autoimmune disease specific.</li> <li>• Internal and external accountability and transparency for autoimmune disease research may improve.</li> <li>• May provide, though to a lesser extent, many of the benefits of a new Institute enumerated in Option 4, with fewer bureaucratic and other costs or controversies.</li> <li>• Establishes direct linkage and interactions with NIH Director and other Offices in the NIH OD.</li> </ul>

**TABLE 7-1** Continued

Cons: Potential Concerns and Disadvantages	<ul style="list-style-type: none"> <li>Would require administrative resources in staffing and infrastructure to conduct strategic planning, cross-IC and cross-governmental collaboration, external communication and dissemination, and stakeholder engagement.</li> </ul>
Feasibility	<ul style="list-style-type: none"> <li>More feasible than the creation of an Institute.</li> </ul>
<b>Option 5a. Create an Office with substantial control over NIH autoimmune disease research and resources</b>	
Pros: Potential Benefits and Advantages	<ul style="list-style-type: none"> <li>Would have funding to stimulate new crosscutting and collaborative autoimmune disease research and enhance workforce development.</li> <li>Would have accountability for funded research activities.</li> </ul>
Costs	<ul style="list-style-type: none"> <li>Moderate to High (in comparison to Option 5b)</li> </ul>
<b>Option 5b: Create an Office without substantial control of NIH autoimmune disease research resources</b>	
Cons: Potential Concerns and Disadvantages	<ul style="list-style-type: none"> <li>The Office would be accountable for its own activities but less so for those controlling resources in other ICs.</li> </ul>
Costs	<ul style="list-style-type: none"> <li>Moderate</li> </ul>

in biomedical research that no single NIH IC can address on its own. Other options would be to model focused autoimmune disease research activities after other cross-NIH activities such as the *All of Us* Research Program,<sup>1</sup> an effort that seeks to advance individualized health care by enrolling 1 million or more participants to contribute their health data over many years, or the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, an effort that seeks to advance the understanding of the brain though development and application of breakthrough neurotechnologies.<sup>2</sup> Such initiatives, however, are generally time-limited and are often focused or limited in topic or scope.

Increased funding directed to certain focused autoimmune disease research activities and initiatives is another alternative. Several focused activities, such as the Autoimmunity Centers of Excellence (ACEs), Accelerating Medicines Partnership® (AMP®) Program including Autoimmune and Immune-Mediated Diseases (AMP® AIM), and the Immune Tolerance Network (Chapter 5) are examples of such focused research activities. Funding to further strengthen the autoimmune disease research

<sup>1</sup> Available at <https://allofus.nih.gov/about/faq> (accessed February 25, 2022).

<sup>2</sup> Available at [https://braininitiative.nih.gov/sites/default/files/pdfs/brain\\_technical\\_one\\_pager\\_1072022\\_508c.pdf](https://braininitiative.nih.gov/sites/default/files/pdfs/brain_technical_one_pager_1072022_508c.pdf).

workforce is a focused activity deserving of additional funds. This could be done with input and collaboration with autoimmune disease-specific and professional societies.

Advantages to increasing funding include a relatively low administrative burden since they would leverage existing mechanisms. Disadvantages include the uncertainty and unpredictability of funding increases that compromises systematic planning for research. Funding increases would be highly contingent on successful advocacy within and outside of NIH, as well as substantial Congressional support.

In addition, in the case of limited new resources, there may be opposition to earmarking funding for autoimmune disease research, and there may be unhelpful competition among ICs and in autoimmune disease research areas. New investments in one area of research may be offset by cuts in another. If funding is not used for collaborative research activities, siloing of research could be accentuated further. Given these considerations, the committee notes that funding by itself is necessary but not sufficient for enhancing the research enterprise for autoimmune diseases; it does not address issues of coordination, prioritization, or workforce development.

### **Option 2a: Coordination by Revitalizing the ADCC**

The ADCC, NIH's current coordinating mechanism for research on autoimmune diseases, was most active between 1998 and 2005, when it produced reports summarizing the state of autoimmune disease research and funding (2000), an autoimmune disease research plan (2002), and a report on progress made in autoimmune disease research (2005). The committee did not identify an implementation plan for the 2005 research plan consisting of goals, strategies, and milestones. Since 2005, reporting to Congress on general progress made on autoimmune disease research has diminished, while the field of autoimmune disease research has expanded and become more complex. The last triennial report to Congress (2016-2018) provides information on highlights of specific research findings in the areas of understanding the biology of autoimmune disease, autoimmune diseases and pregnancy, and successes in improving screening, diagnosis, and treatment.

Currently, resources supporting the ADCC are limited to two staff members from NIAID who carry out ADCC activities as part of their general work responsibilities. In addition, there is no specific funding dedicated to ADCC activities. Based on public records, the ADCC held one public meeting in 2019 and 2020.

Among the advantages of revitalizing the ADCC is that it would not require creating a new entity or developing new relationships within NIH

or with external stakeholders. The experiences gained from developing the 2002 research plan can be applied to developing a new, more robust strategic research and implementation plan. A potential disadvantage to revitalizing the ADCC is that it lacks IC neutrality by virtue of its placement within NIAID. The ADCC also lacks authority and resources to direct or to support the ICs in implementing research associated with a new strategic research and implementation plan. Not only would additional resources be required, but there may be internal reluctance to significantly resource and empower a more robust ADCC.

### **Option 2b: Coordination by Creating an HHS Autoimmune Disease Coordinating Committee**

One alternative that the Department of Health and Human Services (HHS) has used for complex and crosscutting issues is to elevate these issues beyond NIH or other HHS operating divisions. This can be done in multiple ways, including by creating an ad hoc committee, an internal coordinating committee, or an advisory committee at the level of the Secretary. The committee envisions such a committee as an HHS advisory body designed to convene, share, and potentially develop new strategies to tackle this complex problem. Such a body, located within the Office of the Secretary, would help assure that autoimmune disease research and translation to detection, prevention, and care receive deserved attention at NIH and across HHS units, and that these efforts would fully leverage the capabilities of sister agencies.

NIH's participation in a well-run HHS ADCC would allow NIH ICs to be informed on critical ancillary and often practical real-world issues related to autoimmune disease that could be tackled through research. These might include the needs of special populations, including older people, people with disabilities, and racial and ethnic populations. Agencies such as the Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), Health Resources and Services Administration (HRSA), Substance Abuse and Mental Health Services Administration (SAMHSA), as well as the Administration on Aging and the Indian Health Service would have specific expertise in these areas. CDC could provide perspectives on public health dimensions of autoimmune disease. CMS and HRSA could provide expertise on health care issues, and the Food and Drug Administration could advise on regulation and drug approval. SAMHSA could be informed and benefit from NIH research on co-occurring mental health issues related to autoimmune diseases and could provide information on potential areas needing NIH research. An added benefit of elevating this issue to the cabinet level is that it would

ease and enhance engagement with non-HHS agencies such as the Social Security Administration on disability determinations issues that people with autoimmune disease may confront.

While dramatic new policymaking or bold research initiatives might not emerge from the work of a cabinet-level crosscutting committee, important exchanges of information could benefit both the NIH research community and sister agencies. One could also presume that affected individuals and advocacy groups would gain a broader appreciation of these issues through public meetings and other communication efforts.

On the other hand, creating a new crosscutting HHS ADCC can come with costs, added burdens, and frustrations. The downside of broad engagement can be skepticism and the risk of a superficial, rote, or disengaged response. Discussion can lack depth, nuance, or perceived immediate relevance. Cabinet-level engagement also risks politicizing scientific issues. A well-run HHS ADCC would also require staff, funding, and some authority, all of which might be perceived as better spent directly on NIH coordination including enhanced research to fill critical gaps. While the committee believes NIH would benefit from engaging more with sister agencies, it may be that there are less formalized and more issue-specific ways of doing this than the creation of a new HHS body.

### **Option 3: Develop a Congressionally Mandated National Autoimmune Disease/Autoimmunity Research Plan**

The committee considered and believes that there may be significant value in a congressionally mandated National Autoimmune Disease/Autoimmunity Research Plan that could be sited in any one of a number of organizational entities. There is useful precedent for such a plan, perhaps most notably the *National Plan to Address Alzheimer's Disease* (AIM, 2021). NIH is an active participant in providing input to and implementing the *National Plan*. Through the AD+ADRD Research Implementation Milestones database,<sup>3</sup> NIH describes its Alzheimer's research efforts in response to the *National Plan*'s research framework, detailing specific steps and success criteria toward achieving the *National Plan*'s goals. The milestones also note funding initiatives, accomplishments, and highlights of progress toward accomplishing the *National Plan* goals. Congress receives an annual report updating the progress made toward achieving *National Plan* goals (HHS, 2020).

While no analogy between diseases or the state of research for two conditions is ever perfect, there are similarities between Alzheimer's and certain autoimmune diseases in terms of the significant numbers

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<sup>3</sup> Available at <https://www.nia.nih.gov/research/milestones>.

of individuals affected. For example, the estimated number of affected individuals living with Alzheimer's disease is 5.1 million (HHS, 2020), compared with an estimated 14.7 to 23.5 million individuals living with at least one autoimmune disease (NIH, 2005). Yet, understanding of both Alzheimer's disease and autoimmune disease conditions is limited. In some cases, research is in its infancy, treatments are limited, and there are no cures. Most importantly, no overall architecture for Alzheimer's disease research existed before developing the *National Plan*, and one does not exist for autoimmune disease research.

The committee believes that Congress would have to take specific actions for such a plan to yield results. First, those individuals assembling the plan would have to review this committee's and other efforts in order to describe and fully analyze the research portfolio and identify strengths, challenges, and gaps. Second, those assembling the plan would have to devise a process for assembling and executing a plan. This process would involve consulting with internal and independent experts from diverse fields, providing substantial opportunities for public engagement and input, providing regular detailed updates on progress, and convening one or more summits. But most importantly, it would set specific priorities, detailed objectives within those priorities, metrics for evaluating progress, and milestones. Progress reporting would go beyond merely cataloging substantial scientific advances in response to plan goals and objectives. Rather, it would include detailed descriptions of advances that scientists, stakeholders, and other lay people could understand and contextualize.

There are several advantages to a properly conceived and executed plan. First, it brings the imprimatur of Congress, which in turns brings weight, attention, expectation of results, and likely resources. Those funding, overseeing, and otherwise taking a special interest in NIH autoimmune disease research would have a specific stake in achieving certain concrete objectives and outcomes. Moreover, they and other stakeholders would be able to see, and in the case of the public, participate in a process for developing a plan and monitoring its progress and outcomes.

Second, the process would almost certainly enhance communication, coordination, and collaboration, both by virtue of the process and by what it generates. Third, the process would involve a creative review of alternative research paradigms for accelerated progress. These paradigms might suggest new ways of doing business or meta-projects. Fourth, and relatedly, the process of developing a plan might well stimulate researchers to propose, examine, and receive funding for new lines of research. Fifth, it might provide a sense of hope to sufferers and their families that progress is being made in a structured and measurable manner. Efforts that engage the public and offer real transparency often have the ancillary

benefit of demystifying the scientific enterprise and building confidence in the endeavor.

This option is not without potential disadvantages. If not properly structured, progress can give way to process. A plan can raise expectations unreasonably, and focusing on predetermined goals and objectives might cause leaders and researchers to be less attentive to complementary relevant science and research that is happening peripherally or in other domains. NIH's default and highly successful modus operandi, and its remarkable results, often rest more on investigator-initiated research rather than top-down research.

#### **Option 4: Create a New National Institute of Autoimmune Disease and Autoimmunity Research**

The general mission of ICs is to support NIH's overall mission "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability." ICs also support the training of basic and clinical scientists to carry out research and disseminate information on research progress to the public.

The committee considered the creation of a new National Institute of Autoimmune Disease and Autoimmunity Research (NIADAR) that would support and drive innovative, crosscutting autoimmune disease and autoimmunity research through intramural and extramural programs, as well as promote and support the training of an autoimmune disease workforce. Such an Institute would have significant advantages. A new Institute would likely elevate the visibility and status of autoimmune disease within NIH and externally, and it would assure a high-level, constant, broad, and detailed focus on autoimmune disease research. NIADAR would establish a clear focal point for autoimmune disease research for individuals within NIH and for external constituencies. The Institute would function as a clear and empowered convener, coordinator, and accountable focal point for autoimmune disease and autoimmunity research.

To a greater extent than other options considered by the committee, certain critical success factors would need to be addressed for this effort to succeed. A new but underfunded, undefined, weak, or neglected Institute is less desirable than a somewhat diffused effort in well-established and highly functioning ICs. Even if those factors were overcome, establishing a new Institute would come with a number of disadvantages. Creating a new Institute is by definition administratively daunting and would require congressional action. Creating a new Institute would also require a long-term view and patience, neither of which may hold appeal to those

anxious for progress. Thus, creating a new Institute comes with high transaction and opportunity costs, and it could initially increase duplication of effort and even distract from productive research efforts. It might even cause confusion during an initial period of transition.

While reorganizations can bring key people together “under one roof,” they inevitably dislocate key people as well. Moreover, creating new units could engender resistance and resentment from existing entities, neither of which advances the research enterprise. Finally, creating a new Institute risks unrealistically raising expectations about focus, resources, and research outcomes.

#### **Option 5: Create an Office of Autoimmune Disease/Autoimmunity Research within the Office of the Director of NIH**

The committee carefully considered the option of creating an Office of Autoimmune Disease / Autoimmunity Research (OAD / AR) within the OD. The committee found significant merit in this option, provided NIH pursued this option in a way in that would likely succeed. This option is not a new one and was proposed in a bill advanced by then Senator Joe Biden in 1999. The committee found that the 1999 bill addressed several concerns that the committee had raised in its deliberations including the need for a central entity to: promote coordination and cooperation among ICs and other entities, develop an agenda for conducting and supporting autoimmune disease research, promote the appropriate allocation of NIH for autoimmune disease research, report on research activities and identify future research opportunities, and provide leadership on autoimmune disease to HHS, the NIH Director and other relevant agencies.

As governmental units at NIH and elsewhere persuasively argue to Congress, the impact of a research organization is likely to correlate with the extent to which it owns and controls resources. This is particularly true in the case of new entities advising on and negotiating the activities of multiple actors who are already resourced. Given this, the committee considered two configurations for OAD / AR. In the first, OAD / AR would have its own research budget and it would substantially control certain key budgetary decisions about autoimmune disease research activities conducted elsewhere in NIH, the Office of AIDS Research (OAR) serves as a model for this configuration. In the second configuration, while the Office would have certain responsibilities, it would receive only modest or limited resources or authority to carry them out; the Office of Research on Women’s Health serves as a model for this configuration. The committee recommends the former, fully recognizing that budgetary control is among the most sensitive issues within any organization. The committee recognizes that this effort might need to strike some middle ground.

Success will also depend on tailoring OAD/AR to specific and manageable objectives. Furthermore, a successful crosscutting office needs the capacity to suggest and advance creative new scientific approaches, partners, and paradigms. While effective offices recognize the importance of living within institutional cultures and constraints, they can still suggest and direct new ways of doing business that others may not see, have the time or expertise to consider, or the resources to carry out. This, in the committee's view, is how a new OAD/AR within the OD would provide its greatest value.

As noted above, the committee believes successfully implementing any option will depend on careful attention to budget considerations and a variety of other factors critical to success—a substantive and serious focus, a clearly defined strategic vision, and a well-considered level of support for funding and staff. Absent such determinants of success, the committee believes the creation of such an Office would not be a fruitful effort. Because NIH is an institution with world-class expertise, billions of dollars in resources, and extraordinarily high standards, no one benefits when a new organization is created that does not meet those standards. In arriving at this conclusion, the Committee has considered various organizational models for creating an office meeting such standards by examining other Offices within the OD. Based on these reviews, the Committee concludes that OAR can provide a highly desirable model for a new Office of Autoimmune Disease/Autoimmunity Research. This organizational model has provided such important elements for coordinating HIV and HIV-related research through:

- Advice provided to the Director of NIH, HHS, and other entities on HIV and HIV-related research;
- Establishment of research priorities/goals;
- Development and annual evaluation of a strategic plan for HIV and HIV-related research throughout NIH;
- Assurance that funds are invested in the areas of scientific priority and such funding is allocated;
- Oversight, coordination, and management of HIV and HIV-related research (scientific, budgetary, legislative, and policy) in collaboration with other NIH entities (ICs participate in Office advisory bodies);
- Convening stakeholders, encouraging collaboration and catalyzing innovation to address emerging scientific and public health challenges; and
- Including attention to workforce development in strategic goals for HIV and HIV-related research.

Such activities in OAR have led to advances in HIV and HIV-related research ranging from prevention of HIV through a long-acting injectable (incabotegravir) and risk reduction for HIV infection via use of a microbicide (dapivirine) in an intravaginal ring (Office of AIDS Research, 2021). As a central coordinating Office it has been uniquely situated to handle emerging trends and challenges such as the SARS-CoV-2/COVID-19 pandemic by applying knowledge from HIV science. From 2016 to 2021, the NIH HIV research program identified and communicated how HIV research could contribute to an understanding of the COVID-19 pandemic and considered mitigation strategies to assure that the conduct of HIV research would not be negatively affected by the COVID-19 experience. As another example, when SARS CoV-2/COVID-19 emerged, OAR employed internal and external partnerships to develop and disseminate clinical guidelines addressing COVID-19 and HIV. OAR capitalized on the HIV/AIDS Trials Networks to support the pursuit of promising prevention and treatment approaches for COVID-19 through clinical trials (Office of AIDS Research, 2021).

In the area of workforce development, OAR and ICs launched an initiative for inclusion of women and underrepresented populations in the HIV research workforce of the future (Office of AIDS Research, 2021).

Using OAR as a model, the committee believes that a well-configured OAD/AR could be an essential ingredient in further stimulating promising and impactful autoimmune disease and autoimmunity research at NIH that can be translated into clinical practices that will prevent autoimmune disease or improve the lives of those living with autoimmune disease.

The Committee envisions the following responsibilities for the Office:

- A. The Office would devise a process for and lead the collaborative development of a *Strategic Plan* to address opportunities and gaps in scientific knowledge. This would result in an *NIH Strategic Plan for Autoimmune Disease and Autoimmunity Related Research*. The plan would:
  1. Establish both a high-level blueprint and a more detailed research agenda.
  2. Set both high-level national priorities and detailed disease-specific and crosscutting priorities.
  3. Describe a detailed research program and implementation plan for carrying out that agenda.
  4. Work with ICs to identify and promote research opportunities that align with strategic plan goals (e.g., developing solicited requests for applications (RFAs) for crosscutting research grants, promoting Small Business Innovation Research (SBIR)

and Small Business Technology Transfer (STTR) Programs grants).

5. Address autoimmune disease research workforce and training issues, including diversity of the workforce.
6. Provide metrics for evaluating progress and a process for applying those metrics.
7. Examine scientific and organizational barriers to breakthroughs and potential solutions.

In developing and implementing the strategic plan, the Office would actively seek the collaboration and engagement of IC intramural and extramural investigators and other stakeholders. This outreach would serve to catalyze innovation and identify emerging areas of research opportunity. Strengthening outreach could also inform funding for other important research priorities undertaken by various ICs.

In support of strategic planning, the Office, in collaboration with ICs and other stakeholders, should develop a consensus vocabulary that includes both clinically defined autoimmune diseases and autoimmune mechanisms and a list of autoimmune diseases. Such a definition and list of diseases is critical to improve research and data collection and to guide patient care and coordinate communication. Periodic reassessment of the definition and listing of autoimmune diseases, should be undertaken based upon emerging data.

- B. The Office would ensure that funds are invested in the areas of highest scientific priority. The Office would:
  1. Engage in developing detailed autoimmune disease research budgets.
  2. Set budgetary priorities and attempt to align available dollars.
  3. With its own resources, fund certain autoimmune disease research activities including those that are crosscutting, high risk / reward, relevant to special populations, and related to workforce development.
- C. The Office would provide scientific coordination and management of the research program. This would include:
  1. Serving as a focal point for external parties seeking information or providing input on autoimmune disease research opportunities at NIH.
  2. Serving as a convener for emerging and crosscutting science on autoimmune disease. Collaborating with organizations

focused on persons-centered research, such as the Patient-Centered Outcomes Research Institute, and other stakeholders, including industry, disease organizations, patient advocates, and patients and their families in priority setting and research design.

3. Stimulating novel approaches to autoimmune disease research.
  4. Leveraging existing efforts and develop synergies across multiple Institutes, Centers, and scientific disciplines.
  5. Coordinating with the Center for Scientific Review to review assignment guidelines to ensure that autoimmune diseases grants are assigned to the appropriate study sections with optimal representation of experts and expertise, including expertise for reviewing basic science (i.e., tissue culture, animal, translational) and human studies, and evaluate assignment guidelines on an ongoing basis.
  6. Coordinating existing autoimmune disease data collection systems and biorepository resources across NIH; creating a database of such resources to facilitate research collaboration, and coordinating with external databases that may have useful data (e.g., the VA Million Veterans Program, the UK Biobank and industry biorepositories).
  7. Coordinating autoimmune disease research across other HHS agencies and other federal agencies (e.g., AHRQ, CDC, FDA) to promote cohesion in efforts to advance generation of knowledge and care delivery for autoimmune disease.
- D. The Office would conduct or contract for evaluations of ongoing efforts.
- E. The Office would produce annual reports on the progress made on autoimmune disease research activities for Congress. Annual congressional reports can provide key information on priorities and outcomes to enable policymakers to assess the level of funding for autoimmune disease research. Others who could benefit from such information are key stakeholders in the autoimmune disease research enterprise and members of the public.
- F. Building on this report and other relevant reviews, the Office would lead the development of an enhanced information system for autoimmune disease research. The committee's efforts revealed challenges that researchers and policy makers may face in easily accessing, synthesizing, and analyzing relevant research opportunities and results. The committee believes that, consistent

with NIH's existing and excellent information systems, more can be done to allow researchers ready but refined access to research opportunities and ongoing research efforts.

Creating OAD/AR comes with substantial advantages. Virtually all of the advantages enumerated above regarding the creation of an Institute would apply. For example, an Office would raise visibility, provide sustained leadership, and establish a clear focal point for autoimmune disease research within NIH and externally through extramural, intramural, training, communication, and outreach activities. An Office properly constituted and supported could even be leaner and more agile than an Institute.

Proximity to the NIH Director brings obvious advantages, including influence, visibility, and status. Furthermore, the Office would benefit from interactions and collaborations with other Offices in the NIH OD and would be positioned to identify and leverage other NIH-wide research activities that align with the autoimmune disease research agenda. The Office would both bring and benefit from a crosscutting, independent perspective that would allow more objective priority setting, measurement, and evaluation.

OAD/AR would independently advocate for and promote transparency, and it would establish a framework for accountability among relevant ICs. This would build goodwill among stakeholders that in turn would strengthen support for the research endeavor. Finally, fewer costs and controversies generally come with creating offices than with creating new institutes.

The committee acknowledges that beyond the caveats raised in the introduction above, creating an Office is not without potential challenges. First, though more modest than those required by a new Institute, creating a new Office would require significant resources for infrastructure, robust staffing, and the capacity to function nationally and internationally as a convener, broker, and communication hub. Second, it would likely require new funding to stimulate new crosscutting and collaborative autoimmune disease research and enhance workforce development. Third, the more authority and resources it is granted, the more opposition it may encounter. Opposition may bring some disruption, some of which may be unproductive, and resistance that may undercut collaboration.

On balance, the committee believes that the advantages of creating an Office significantly outweigh the disadvantages. Such an Office has potential promise and impact in expanding both the frontiers and near-term impacts of autoimmune disease research. The committee believes

that creating OAD/AR is the best alternative for strengthening autoimmune disease research at NIH.

## RECOMMENDATIONS

As discussed above, the committee considered five options for enhancing autoimmune disease research and resulting outcomes: increased funding, two options for coordinating research, establishing a national strategic plan, establishing a new Institute, and creating a special office for autoimmune disease research. With the caveats noted above, the committee believes that a well-configured Office of Autoimmune Disease/Autoimmunity Research could be an essential ingredient in further stimulating promising and impactful autoimmune disease and autoimmunity research at NIH that can be translated into clinical practices that will prevent autoimmune diseases or improve the lives of those living with autoimmune disease.

**Recommendation 1: The Director of the National Institutes of Health should create an Office of Autoimmune Disease/Autoimmunity Research within the Office of the Director.**

Acknowledging that creating an OAD/AR may take some time, the committee makes two specific recommendations related to data collection that could be implemented independent of the Office by ICs, one independently and the other in collaboration with other ICs. First, progress on autoimmune disease requires substantially more sophisticated and refined epidemiology on the individual and aggregate burden of autoimmune disease. The extant knowledge base is growing, but there are important gaps, including incidence and prevalence trends, comprehensive evaluations of the risk factors and the burden (including direct and indirect costs) of these diseases, the impact on different populations, the trajectory of these diseases from the period before disease manifests through the life course, and the impact of specific treatments and interventions.

The committee found a lack of long-term (20 years or more) population-based epidemiology studies on autoimmune disease. Such studies would allow for assessing trends, identifying differences among population subgroups, and determining the prevalence and incidence of under-researched autoimmune diseases and conditions, such as celiac disease. The National Cancer Institute's Surveillance, Epidemiology, and End Results Program, which provides information on cancer incidence and survival in the United States, is a model for such studies that already exists at NIH.

**Recommendation 2: The National Institutes of Health should establish long-term systems to collect and ensure optimum usability of population-based surveillance and epidemiological data (e.g., incidence, prevalence) on autoimmune diseases and measures of autoimmunity (e.g., autoantibodies, inflammation) and support the optimization of existing data sources.**

The committee also found that few studies exist that are able to provide information on the long-term progression of autoimmune disease beginning in the period before disease manifests through the life course. Such studies would allow for a greater understanding of the heterogeneity of disease expression and changes with time and over various life stages. Such studies could be designed to address a wide variety of disease outcomes and health effects.

Establishing population cohorts is critical for studying mechanisms leading to autoimmune diseases. Early life exposures and timing of these exposures influence health at different life stages at a population and individual patient level. Autoimmune diseases are long-lasting and heterogeneous conditions for which manifestations and coexisting morbidities change over time. It is essential to support long-term (10–20+ years) patient cohort studies. Such studies would provide understanding of opportunities for developing clinical treatments and behavioral interventions.

**Recommendation 3: The National Institutes of Health should support the development of population cohorts that extend from the period before disease manifests to the development of symptoms and disease, and should support patient cohorts that will allow the examination of the progression, coexisting morbidities, and long-term (20+ years) outcomes of autoimmune diseases. Data collection should include, but need not be limited to:**

- Genome-wide association
- Environmental and occupational exposures such as respirable silica, vitamin D and iodine, viruses, and smoking
- Autoantibody, cytokine, and T cell assays, particularly in new-onset disease
- Response to therapeutic interventions, including timing of treatment (e.g., to assess whether early treatments prevent disease progression)
- Development of co-occurring autoimmune diseases

Finally, to address the research gaps outlined throughout this report, a comprehensive national research agenda for autoimmune diseases is required. Achieving this objective will require coordination and

collaboration among researchers, research groups, and stakeholders as well as the dedicated pursuit of research that defines autoantibodies that predict and diagnose autoimmune diseases; identifies common mechanisms in inflammation; determines gene–environment interactions within and across autoimmune diseases; examines the role of environmental exposures on autoimmune diseases; elucidates disparities and their determinants; determines the impact of coexisting morbidities and complications of autoimmune diseases on clinical outcomes, functional outcomes, quality of life, and health care utilization; and explores the effect of interventions to mitigate impact of coexisting morbidities and complications for patients with autoimmune disease across the lifespan.

During the course of researching Chapters 3 and 4, the committee assembled a list of research needs based on committee judgment. The list below is not intended to be comprehensive. However, it is indicative of the kinds of research needed, and by itself is far-reaching in terms of the kinds of research and disciplines required as well as the many diseases included in the autoimmune disease category. The committee believes that a robust effort will be required to coordinate creation of a comprehensive national research agenda that incorporates the thinking of associated ICs and other stakeholders, and as such illustrates the role that an OAD/AR could fill as no other currently existing entity could.

**Recommendation 4: The National Institutes of Health should provide funding and support for a national autoimmune disease research agenda that addresses key gaps identified by the committee. Prioritized research streams should include, but need not be limited to, clinical and basic research that addresses the research streams below.**

Heterogeneity in autoimmune diseases takes many forms, which could range from differences in symptom presentation and disease progression, as seen in persons with systemic lupus erythematosus, to severity of disease, as observed in myocarditis in men compared with women, to varying responses to the same therapy.

**Dissect heterogeneity across and within autoimmune diseases to decipher common and disease-specific pathogenic mechanisms.**

- Examine common innate inflammatory pathways (e.g., damage-associated molecular patterns, pathogen-associated molecular patterns, pattern recognition receptors, inflammasomes, and associated signaling pathways), dysregulated cellular processes, and altered metabolism across multiple autoimmune diseases to understand the biologic mechanisms underlying

**development, progression, remission, and exacerbation of autoimmune diseases in children and adults**

- Apply machine learning methods that combine layers of “omics” data (e.g., genomics, proteomics, metabolomics) to generate new mechanistic hypotheses and inform discovery of novel drug targets
- Elucidate mechanisms by which sex-specific factors (such as hormones, X and Y chromosomes, birth control products, endocrine disrupting chemicals) influence autoimmune disease, examining the effect of puberty, pregnancy, and menopause to understand sex differences in autoimmune diseases
- Identify autoantigens across autoimmune diseases using new technologies that allow T-cell receptors identified by single cell RNA sequencing from tissue to be interrogated without bias transfecting mRNA libraries into reporter antigen presenting cells
- Dissect molecular mechanisms associated with poor outcomes
- Design research that bridges animal models and human studies to better understand common mechanisms in inflammation for specific autoimmune diseases

Researching less common autoimmune diseases can be difficult owing to smaller pools of persons affected. At the same time, identifying genetic variants, for example, could reveal insights that might be applied to more common diseases. Persons suffering from rare diseases that are associated with severe illness and or/early mortality are of particular concern.

**Study rare autoimmune diseases and develop supporting animal models.**

- Study autoimmune diseases that affect fewer individuals but often have a high morbidity/earlier mortality to reveal novel, shared, or dominant molecular pathways and novel or improved therapeutic options
  - Dominant pathways in the less common autoimmune diseases may reveal shared molecular pathways with other autoimmune diseases to facilitate drug-repurposing, rapid trials, and possible therapies that could rapidly impact clinical care
- Develop animal models to better understand the mechanisms of rare autoimmune disease

Chapter 4 reviewed a variety of signals being explored as biomarkers to predict disease, confirm diagnosis, and predict flares of disease.

Further investigation of these and novel signals can inform preventive and therapeutic strategies.

**Define autoantibodies and other biomarkers that can diagnose and predict the initiation and progression of autoimmune diseases.**

- Determine the pathophysiological relationship of antibodies to autoimmune disease—for example, which autoantibodies are biomarkers of autoimmune diseases, which are effectors, and the reasons for the differences
- Determine the temporal relationship of antibodies to autoimmune disease—for example, how and why some autoantibodies appear decades before clinical illness and others appear simultaneously with first symptoms
- Understand differences in autoantibody profiles by age, sex, sex-and-age, race, ethnicity, and ancestry for individual autoimmune diseases and in relation to their ability to predict and diagnose autoimmune disease
- Examine whether infections (e.g., SARS-CoV-2) and/or chemicals (e.g., bisphenol A) influence autoantibody levels/types and/or immune complex formation that are diagnostic or pathological for autoimmune diseases
- Explore the pipeline for development and validation of autoantibodies as disease biomarkers and surrogate endpoints of disease
- Identify novel biomarkers and complex “signatures” that predict and diagnose autoimmune diseases including cytokines, microRNAs and other markers

As discussed in Chapter 2 and Chapter 4, genetics, and particularly gene variants, environmental exposures, and timing interact to increase or blunt an individual’s susceptibility to autoimmune diseases. Identifying the biological functions of gene variants and the effects of environmental exposures on their functions over time could reveal new avenues for care.

**Determine the biologic functions of genetic variants and gene-environment interactions within and across autoimmune diseases using novel, cutting-edge technologies.**

- Study early-onset (e.g., childhood-onset) and rare autoimmune diseases to identify pathologic genetic variants and potential mechanistic insights
- Systematically map genetic variants of individual autoimmune diseases to biologic functions in different populations in order to (1) translate genotype to phenotype, (2) define immune

**pathways that may predict response to treatment, and (3) inform understanding of the effect of environmental exposure in autoimmune diseases**

- Understand genomic and pharmacogenomic data as they relate to the individual, that are disease specific, or provide insight across multiple autoimmune diseases
- Explore chimeric antigen receptor-T cell/natural killer cell therapies to benefit immune regulation
- Use and improve artificial intelligence, computational science, and other technologies to understand gene–environment interactions

Social determinants of health such as trauma, including cumulative childhood stress as a result of adverse childhood experiences, can increase the risk of autoimmune disease (Dube et al., 2009; Roberts et al., 2017). Similarly, the trauma and the dust clouds of the September 11, 2001 attack have been implicated in the increased risk of systemic autoimmune disease in exposed persons (Miller-Archie et al., 2020). The mechanisms by which social determinants and environmental exposures act alone and together to affect the risk for and course of autoimmune disease over the life span should be investigated using systematic approaches whenever possible.

**Examine the role of environmental exposures and social determinants of health in autoimmune diseases across the lifespan.**

- Systematically examine the effect of environmental exposures (e.g., chemical, infectious, dietary) and social determinants of health in children and adults, including stress, for individual and/or multiple autoimmune diseases, including disease flares
- Determine the effect of environmental exposures on immune pathways in patients and animal models of autoimmune disease
- Utilize a life-course approach along with advanced methodologies (e.g., computational science) to identify and examine the potential effect of interacting co-exposures that may increase susceptibility to disease, and to understand how these factors affect onset, progression, and severity of disease
- Conduct a systematic investigation of the effects of nutrients, dietary antigens, exercise, aging, and microbiome in normal tissue development and homeostasis in the pre-clinical phase of disease and during disease and recovery
- Explore novel methodologies to identify distinct and interacting biological and biopsychosocial factors contributing to observed sex/gender differences in autoimmune diseases, including the effect of puberty, menopause, and pregnancy on autoimmune diseases

As indicated in Chapters 3 and 4, individuals frequently develop more than one autoimmune disease at a time as well as complications and other morbidities. The data on co-occurring autoimmune diseases focuses only on a limited number of diseases. Evaluating the epidemiology and risks for developing other morbidities, identifying those at greatest risk, assessing the impacts of coexisting morbidities, and developing interventions to prevent or ameliorate these could greatly improve patient care.

**Determine the impact of coexisting morbidities, including co-occurring autoimmune diseases and complications of autoimmune diseases, across the lifespan, and develop and evaluate interventions to improve patient outcomes.**

- Investigate the occurrence of and risk factors for disease complications (e.g., functional impairment, disability, growth impairment), co-occurring autoimmune diseases, coexisting morbidities (e.g., cardiovascular disease, cancer), and psychosocial conditions (e.g., fatigue, depression, pain)
- Investigate the effects of complications and coexisting morbidities on clinical outcomes (e.g., adherence to therapy, disease activity, disease damage), functional outcomes (activity and participation in daily and community life, education and work status), health-related quality of life, and healthcare utilization and costs.
- Conduct research to improve understanding of the long-term consequences of autoimmune diseases in children
- Develop and test treatment models, targeting those at highest risk, that prevent, detect, and address complications and coexisting morbidities in persons living with autoimmune disorders, incorporating chronic disease self-management strategies and other approaches
- For complications for which there are no highly effective treatments, such as pain and fatigue, develop, identify, and test new therapies
- Develop and test interventions to improve or address lack of or inadequate social support in order to improve symptom and disease management and daily life, including interventions for parents of children with autoimmune disorders

There are disparities in who develops autoimmune diseases as well as how the diseases progress; among the causes for disparities are differences in living environments, access to and affordability of care, and even provision of care. Researchers have observed, for example, that Hispanic

patients and patients in the U.S. South with autoimmune disease-related kidney failure are less likely to receive kidney transplants than non-Hispanic patients or patients in the U.S. West and Northwest (Costenbader et al., 2011; Knight et al., 2014). Research to identify the causes of and risks of disparities, interventions to mitigate them, and the most effective way to implement mitigations is needed, particularly in groups who receive suboptimal care and are underrepresented in clinical populations.

**Foster research to advance health equity for all autoimmune disease patients.**

- Investigate genetic, biological, and social determinants, and environmental mechanisms of autoimmune diseases in different racial, ethnic, and other underrepresented groups, as well as across sexes and over the lifespan
- Identify individuals at high risk of autoimmune diseases and implement prevention strategies
- Investigate disparities and determinants of disparities in disease stage at presentation and progression of disease, including complications, coexisting morbidities, functional impairments, and disability
- Explore novel methodologies to identify distinct and interacting biological and biopsychosocial factors contributing to observed sex differences in autoimmune diseases
- Collaborate with consumers, community-based organizations, and other partners to develop and evaluate health care delivery and/or policy interventions to address identified disparities and generate evidence to support their feasibility, sustainability, and dissemination
- Build long-term partnerships between patients, communities, clinicians, and scientists to increase participation of underserved populations in interventional clinical trials and other clinical and translational research studies
- Conduct dissemination/implementation research to determine best practices and to improve outcomes for all
- Conduct research on how to increase recruitment of underserved populations in clinical research, and in interventional clinical trials in particular
- Conduct research on how best to target interventions for patients with worse outcomes and/or underserved populations

Chapter 2 noted that rates of many autoimmune diseases are rising. Chapter 3 revealed that there are inadequate data on the financial costs of autoimmune diseases. For diseases where good data are available such

as inflammatory disease and celiac disease, the estimated costs are high. As these costs will impact public health budgets, research to define costs should be undertaken as findings could inform research priorities.

**Assess the direct and indirect costs of autoimmune diseases.**

- Examine insurance claim data to assess inpatient, emergency room, outpatient, physician visit, pharmacy (including disparities between different therapies), laboratory, and medical device costs associated with autoimmune diseases
- Examine the costs of lost wages, job turnover, and other work-productivity issues
- Examine the costs of premature mortality
- Examine the costs of associated home care and child care

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## Appendix A

### Committee Member and Staff Biographies

**Bernard M. Rosof, M.D.** (*Chair*), is a professor in the Department of Medicine at the Zucker School of Medicine at Hofstra/Northwell. He is a member, and past Chair, of the Board of Directors of Huntington Hospital (Northwell Health). A practicing internist and gastroenterologist for nearly 30 years, he is at the forefront of national initiatives in the areas of quality and performance improvement. He served on the Board of Directors of the National Quality Forum (NQF) and as co-Chair of the National Priorities Partnership (NPP) convened by the NQF to set national priorities and goals to transform America's healthcare. Dr. Rosof is a past Chair of the Physician Consortium for Performance Improvement convened by the American Medical Association to lead efforts in developing, testing, and implementing evidence-based performance measures for use at the point of care. He is a Master of the American College of Physicians and Chair Emeritus of the Board of Regents of the American College of Physicians. He also served as a member of the Clinical Performance Measurement Committee of the National Committee for Quality Assurance and Chair of the Physician Advisory Committee for UnitedHealth Group. He has chaired committees for the New York State Department of Health and the National Academies of Sciences, Engineering, and Medicine, and is the Board Chairman of the Institute for Exceptional Care. Dr. Rosof is on the editorial board of the *American Journal of Medical Quality* and has published extensively in the peer-reviewed medical literature. He received his M.D. from New York University and completed a fellowship in gastroenterology at Yale School of Medicine.

**Glinda S. Cooper, Ph.D.**, is an internationally recognized expert in environmental epidemiology and women's health. During her tenure in the Epidemiology Branch of the National Institute of Environmental Health Sciences from 1993 to 2006, she developed and directed a multidisciplinary research program focusing on occupational and hormonal influences on lupus and other autoimmune diseases. This research program helped establish our understanding of the effects of occupational and environmental exposures, particularly silica dust, on autoimmune diseases. Dr. Cooper also led efforts to create and implement an evidence-based, systematic review framework for the evaluation of chemical hazards at the National Center for Environmental Assessment in the U.S. Environmental Protection Agency, and conducted the evaluation of immune-related and reproductive health effects of solvents, pesticides, and other environmental exposures. As the Director of Science and Research at the Innocence Project from 2016 to 2021, Dr. Cooper focused on efforts to strengthen the scientific basis of forensic disciplines and on evidence-based reforms aimed at reducing wrongful prosecutions and convictions. Dr. Cooper received a Ph.D. from the Department of Epidemiology of the University of North Carolina at Chapel Hill and a Sc.M. in health policy and management from the Harvard School of Public Health. She has published more than 100 peer-reviewed papers based on her research and has been an invited speaker and workshop organizer at numerous international and national meetings.

**Deidra C. Crews, M.D., Sc.M.**, is a professor of medicine in the Division of Nephrology at the Johns Hopkins University School of Medicine. Dr. Crews holds appointments with the School of Nursing; the Welch Center for Prevention, Epidemiology and Clinical Research; the Center on Aging and Health; and the Center for Health Equity, where she is Deputy Director. Her research focuses on addressing disparities in the care and outcomes of kidney disease and hypertension, with a special emphasis on social drivers of these disparities. An elected member of the American Society for Clinical Investigation, Dr. Crews has received numerous awards for her research contributions, including the 2018 Johns Hopkins University President's Frontier Award. She was a National Academy of Medicine (NAM) Emerging Leader in Health and Medicine Scholar and was the inaugural Gilbert S. Omenn Fellow of the NAM. A Master of the American College of Physicians (ACP), in 2019, Dr. Crews received the W. Lester Henry Award for Diversity and Access to Care from the ACP and the Distinguished Leader Award from the American Society of Nephrology.

**William R. Duncan, Ph.D.**, is Vice Provost for Research Emeritus at East Tennessee State University. Previously he was Chief Operating Officer and Chief Scientific Officer of the Baylor Research Institute. At the National Institute of Allergy and Infectious Diseases, he served as Associate Director of the Therapeutics Research Program in the Division of AIDS beginning in 1993, and then served as Deputy Director of the Division of Allergy, Immunology and Transplantation from 2002 to 2004. He has extensive experience developing and administering national and international research programs, promoting the development of therapeutic agents and diagnostic tools for the treatment of cancer, infectious diseases, and autoimmune diseases. He received his Ph.D. in immunology from the University of Texas Health Science Center at Dallas.

**DeLisa Fairweather, Ph.D.**, is associate professor of medicine and Director of Translational Research for the Department of Cardiovascular Diseases at Mayo Clinic. Her laboratory conducts translational research focused on finding individualized therapies and improved diagnosis for chronic inflammatory diseases. In addition to an interest in myocarditis, dilated cardiomyopathy, and heart failure, Dr. Fairweather specializes in how sex differences in inflammation caused by environmental exposures lead to chronic inflammatory disease, including rheumatic autoimmune diseases, cardiovascular disease, cancer, and lung disease. She has served as a Councilor for the Organization for the Study of Sex Differences for three separate terms over 10 years. She currently has National Institutes of Health funding for three studies on myocarditis. She was a standing member of the Atherosclerosis and Inflammation of the Cardiovascular System Study Section at NIH from 2014 to 2020, and she serves on the Medical Advisory Board for the Myocarditis Foundation. After earning a Ph.D. in microbiology and immunology at the University of Western Australia, she completed a postdoctoral fellowship in immunology in the laboratory of Noel R. Rose, M.D., Ph.D., at Johns Hopkins University School of Medicine. She is a Co-Investigator and Leader of the Mayo-led U.S. Food and Drug Administration/Biomedical Advanced Research and Development Authority–funded Expanded Access Program (EAP) providing convalescent plasma to patients with COVID-19.

**Sonia Friedman, M.D.**, is an associate professor of medicine at Harvard Medical School and Director of Women's Health at the Crohn's and Colitis Center at Brigham and Women's Hospital in Boston. She is an adjunct Professor of Clinical Epidemiology at the University of Southern Denmark in Odense, Denmark. Dr. Friedman completed her undergraduate degree in biology at Stanford University and her M.D. at Yale Medical School. She did her medical internship and residency at University of Pennsylvania

and her gastroenterology fellowship at Mount Sinai Medical Center in New York City. She is an expert on inflammatory bowel disease (IBD), and her research interests include IBD and fertility and pregnancy. She is the co-author of the chapter on IBD in *Harrison's Principles of Internal Medicine* and is a frequent speaker and invited regional and national lecturer on the management of IBD. Dr. Friedman is the Deputy Editor of the journal *Inflammatory Bowel Diseases* and is on the *Gastroenterology, Alimentary Pharmacology and Therapeutics* and *Digestive Diseases and Sciences* editorial boards. She is a member of the Crohn's and Colitis Foundation Unbiased Peer Review Task Force, the Crohn's and Colitis Foundation Clinical Research Alliance, and the organizing committee of the Crohn's and Colitis Foundation Congress. She has received a recent Crohn's and Colitis Foundation Senior Research Award as well as an American College of Gastroenterology Clinical Research Award to continue her work on reproductive health in IBD.

**Lisa I. Iezzoni, M.D., M.Sc.**, is a professor of medicine at Harvard Medical School based at the Health Policy Research Center at the Mongan Institute at Massachusetts General Hospital. She has conducted health services research for more than 35 years, focusing on two primary areas: risk adjustment methods for predicting cost and clinical outcomes of care, and health care experiences and outcomes of persons with disabilities. Dr. Iezzoni spent 16 years at Boston's Beth Israel Deaconess Medical Center, before moving in 2006 to Massachusetts General Hospital, where from 2009 to 2018 she served as director of the Mongan Institute for Health Policy. She edited *Risk Adjustment for Measuring Health Care Outcomes*, now in its fourth edition; her most recent book is *Making Their Days Happen: Paid Personal Assistance Services Supporting People with Disability Living in Their Homes and Communities*, published in 2022. She is a member of the National Academy of Medicine. Dr. Iezzoni received her M.Sc. from the Harvard School of Public Health's Health Policy and Management program and her M.D. from Harvard Medical School.

**Andrea M. Knight, M.D., M.S.C.E.**, is an associate professor of pediatrics at the University of Toronto Temerty Faculty of Medicine, and a staff physician in the Division of Rheumatology at the Hospital for Sick Children in Toronto, where she is an associate scientist in the Neurosciences and Mental Health Program of the Research Institute. She is also an adjunct assistant professor of pediatrics in the associated faculty of the Perelman School of Medicine at the University of Pennsylvania. Dr. Knight's research focuses on mental health in youth with rheumatologic conditions, with an emphasis on neuropsychiatric function in childhood-onset systemic lupus erythematosus (cSLE). She has investigated the burden of

psychiatric morbidity and strategies to improve comprehensive care for youth with SLE and other rheumatologic disease. She is also investigating the impact of cSLE on brain structure, function, and development. She is currently co-leading a Centers for Disease Control and Prevention–funded project investigating epidemiology and outcomes in cSLE. Her work has been recognized by her receipt of the Mary Betty Stevens M.D., Young Investigator Prize from the Lupus Foundation of America (LFA) and the Dubois Memorial Lectureship from the American College of Rheumatology. She currently serves as chair of the Lupus Committee and co-leader of the Mental Health Workgroup for the Childhood Arthritis and Rheumatology Research Alliance, member of the LFA Medical Scientific Advisory Council, and member of the Lupus Research Alliance Scientific Review Committee. Dr. Knight received her M.D. from the College of Physicians and Surgeons of Columbia University. She completed a residency in pediatrics and a fellowship in pediatric rheumatology at CHOP. She earned her M.S.C.E. from the University of Pennsylvania.

**Scott M. Lieberman, M.D., Ph.D.**, is associate professor of pediatrics in the Division of Rheumatology, Allergy and Immunology at Carver College of Medicine, University of Iowa. His research goals are to understand the earliest immunologic events in the development of organ-specific autoimmunity to identify potential targets for better diagnosis and treatment of these diseases. The main focus of his laboratory is the role of T cells in the initiation of lacrimal and salivary gland autoimmunity characteristic of Sjögren's disease. He currently has National Institutes of Health funding for a study on the role of cytokines in T-cell dysregulation in lacrimal gland autoimmunity. He also cares for children with rheumatic diseases and participates in efforts to better understand Sjögren's in children through an international collaborative workgroup. He has co-authored several book chapters on rheumatic disease manifestations in children including, most recently, the chapter on Sjögren's in children in *Sjögren's Syndrome: A Clinical Handbook* (Elsevier). He received the Arthritis Foundation's Stewart J. McCracken Award for excellence in the field of arthritis research, and he was awarded an American Association of Immunologists Careers in Immunology Fellowship. He earned his Ph.D. in immunology and his M.D. at the Albert Einstein College of Medicine. He performed a residency in pediatrics (ABP Special Alternative Pathway) at the Children's Hospital of Philadelphia, where he also completed a fellowship in pediatric rheumatology.

**Michael D. Lockshin, M.D.**, is the director of the Barbara Volcker Center for Women and Rheumatic Disease at Hospital for Special Surgery (HSS) in New York and professor of medicine and obstetrics-gynecology at

Weill Cornell Medicine. As a medical student he cared for a seriously ill pregnant woman with systemic lupus erythematosus (SLE), and he has focused his career on patients with this disease. He was one of the first physicians to associate the newly discovered antiphospholipid antibody with pregnancy complications. Dr. Lockshin has had a long-standing interest in the overlap of autoimmune diseases such as SLE, multiple sclerosis, and thyroid disease, and in sex differences in disease incidence. He is also working to create consensus to systematize approaches for confronting diagnostic uncertainty for patients with conditions that do not fall within clear diagnostic criteria. A member of the faculty of Weill Cornell Medical College and a staff rheumatologist at HSS and New York Hospital (now Weill Cornell Medicine) from 1970 to 1989, he became Extramural Director, then Acting Director, of the National Institute of Arthritis and Musculoskeletal and Skin Diseases in 1989. He returned to HSS in 1997 to head the Barbara Volcker Center. He also served as an Epidemic Intelligence Service Officer in the U.S. Public Health Service of the Communicable Disease Center (now Centers for Disease Control), where he focused on environmental causes of rheumatic illnesses. Dr. Lockshin has served as editor-in-chief of *Arthritis and Rheumatism*, rheumatology's premier journal. He has served on several National Academy of Medicine committees. Dr. Lockshin received his M.D. from Harvard Medical School, and he completed his medical residency at Second (Cornell) Medical Service at Bellevue Hospital and Memorial Sloan Kettering Cancer Center and his rheumatology fellowship at Columbia-Presbyterian Hospital (now New York-Presbyterian/Columbia University Irving Medical Center). He has written three lay language books that discuss how doctors and patients interact regarding chronic illnesses and diagnostic uncertainty.

**Jill M. Norris, Ph.D., M.P.H.**, is professor and chair of the Department of Epidemiology in the Colorado School of Public Health at the University of Colorado Denver Anschutz Campus. Dr. Norris' research has focused on the relationship between diet and other environmental exposures and the development of autoimmune diseases—including type 1 diabetes, celiac disease, rheumatoid arthritis, and lupus—using longitudinal cohort studies in which genetically at-risk individuals are followed for the appearance of autoantibodies and subsequent progression to clinical disease. She has taken part (as principal investigator or co-investigator) in multiple National Institutes of Health–funded studies of autoimmune diseases, and she is currently funded to examine dietary, metabolomic, epigenetic and transcriptomic factors involved in the progression from autoimmunity to type 1 diabetes. She was a member of the National Institute of Environmental Health Sciences Expert Panel to Examine the Role of the Environment in the Development of Autoimmune Disease. She was a

contributor to *Diabetes in America* (3rd ed., 2016–2018), published by the National Institute of Diabetes and Digestive and Kidney Diseases. She is an elected member of the American Epidemiological Society. She received her M.P.H. and Ph.D. in epidemiology from the University of Pittsburgh Graduate School of Public Health.

**Emily C. Somers, Ph.D., Sc.M.**, is associate professor of internal medicine-rheumatology, of environmental health sciences, and of obstetrics and gynecology at the University of Michigan Schools of Medicine and Public Health. She specializes in autoimmune diseases, particularly lupus, and her work spans epidemiologic, clinical, and translational research, including the design and conduct of clinical trials. She has performed leading population-based studies of lupus epidemiology in the United Kingdom, Denmark, and United States. Major research interests include epidemiology, comorbidities, and public health impact of rheumatic and autoimmune diseases; clinical epidemiology of systemic lupus erythematosus (SLE), including studies of subclinical cardiovascular disease in SLE and gene expression-based molecular classification of lupus nephritis; and pharmacoepidemiologic issues in autoimmune disease. Her work in pharmacoepidemiology has characterized risk of drug-induced lupus, as well as developmental outcomes among offspring of mothers whose pregnancies occurred in the presence of SLE. She has received National Institutes of Health funding and currently receives U.S. Centers for Disease Control and Prevention funding for research investigating early life exposures to metals and development of immune dysfunction. She received her Sc.M. and Ph.D. in epidemiology from the London School of Hygiene and Tropical Medicine, and from the Johns Hopkins School of Hygiene and Public Health, respectively.

**Barbara G. Vickrey, M.D., M.P.H.**, is professor and System Chair of Neurology at the Icahn School of Medicine at Mount Sinai. She specializes in translating clinical evidence into improvements in routine medical practice to improve patient health. Among her accomplishments are demonstrating that collaboration among health care systems, community organizations, and caregivers can improve quality of care and outcomes for patients with dementia. She has designed health care delivery innovations ranging from better control of post-stroke risk factors in underserved populations to new ways to care for veterans with Parkinson's disease. Dr. Vickrey is a member of the National Academy of Medicine. Dr. Vickrey served for 25 years on the faculty of the University of California, Los Angeles (UCLA), where she was professor of neurology and Director of the departmental Health Services Research Program. She was also Associate Director for Research at the Greater Los Angeles Veterans

Administration Parkinson's Disease Research, Education and Clinical Center. Dr. Vickrey earned her M.D. at Duke University School of Medicine and her M.P.H. at the UCLA School of Public Health. She completed postgraduate clinical training in medicine and neurology at the University of Washington in Seattle, and then research fellowships in the Robert Wood Johnson Clinical Scholars Program and the Rand/UCLA Center for Health Policy Study.

## STAFF

**Rose Marie Martinez, Sc.D.**, is the Director of the Board on Population Health and Public Health Practice (1999–present) at the National Academy of Sciences, Engineering, and Medicine. The Board conducts evidence-based studies that help shape health policy at the federal, state and local levels. Prior to joining the National Academies, Dr. Martinez was a Senior Health Researcher at Mathematica Policy Research (1995–1999) where she conducted health policy research. Dr. Martinez is a former Assistant Director for Health Financing and Policy with the U.S. General Accounting Office where she directed evaluations and policy analysis in the area of national and public health issues (1988–1995). Her experience also includes 6 years directing research studies for the Regional Health Ministry of Madrid, Spain (1982–1988). Dr. Martinez received the degree of Doctor of Science from the Johns Hopkins School of Hygiene and Public Health.

**Kristin E. White** is an associate program officer in the Health and Medicine Division of the National Academies. She worked for several years as a medical editor and writer, working on Continuing Medical Education programs and other forms of medical education. She received an A.B. from Princeton University.

**Dara Rosenberg, M.P.H.**, is a research associate in the Health and Medicine Division on the Board of Population Health and Public Health Practice. Before joining the National Academies, Ms. Rosenberg was an epidemiologist at a local health department. She has experience with communicable disease investigations, public health emergency preparedness, and data analysis, specifically with STI/HIV and COVID-19 data. She completed her B.S. in health sciences at New York Institute of Technology and has a Master of Public Health in epidemiology from The George Washington University.

## Appendix B

### List of Autoimmune Diseases

Autoimmune Association Autoimmune Disease List (Autoimmune Association, 2021).

Achalasia	Autoimmune urticaria
Addison's disease	Axonal & neuronal neuropathy (AMAN)
Adult Still's disease	Baló disease
Agammaglobulinemia	Behcet's disease
Alopecia areata	Benign mucosal pemphigoid (Mucous membrane pemphigoid)
Amyloidosis	Bullous pemphigoid
Ankylosing spondylitis	Castleman disease (CD)
Anti-GBM / Anti-TBM nephritis	Celiac disease
Antiphospholipid syndrome	Chagas disease
Autoimmune angioedema	Chronic inflammatory demyelinating polyneuropathy (CIDP)
Autoimmune dysautonomia	Chronic recurrent multifocal osteomyelitis (CRMO)
Autoimmune encephalitis	Churg-Strauss syndrome (CSS) or Eosinophilic granulomatosis (EGPA)
Autoimmune hepatitis	Cicatricial pemphigoid
Autoimmune inner ear disease (AIED)	Cogan's syndrome
Autoimmune myocarditis	
Autoimmune oophoritis	
Autoimmune orchitis	
Autoimmune pancreatitis	
Autoimmune retinopathy	

Cold agglutinin disease	Juvenile myositis (JM)
Complex regional pain syndrome (formerly known as reflex sympathetic dystrophy)	Kawasaki disease
Congenital heart block	Lambert-Eaton syndrome
Coxsackie myocarditis	Lichen planus
CREST syndrome	Lichen sclerosus
Crohn's disease	Ligneous conjunctivitis
Dermatitis herpetiformis	Linear IgA disease (LAD)
Dermatomyositis	Lupus
Devic's disease (neuromyelitis optica)	Lyme disease chronic
Discoid lupus	Meniere's disease
Dressler's syndrome	Microscopic polyangiitis (MPA)
Endometriosis	Mixed connective tissue disease (MCTD)
Eosinophilic esophagitis (EoE)	Mucha-Habermann disease
Eosinophilic fasciitis	Multifocal motor neuropathy (MMN) or MMNCB
Erythema nodosum	Multiple sclerosis
Essential mixed cryoglobulinemia	Myasthenia gravis
Evans syndrome	Myelin oligodendrocyte glycoprotein antibody disorder
Fibromyalgia	Myositis
Fibrosing alveolitis	Narcolepsy
Giant cell arteritis (temporal arteritis)	Neonatal lupus
Giant cell myocarditis	Neuromyelitis optica / devic disease
Glomerulonephritis	Neutropenia
Goodpasture's syndrome	Ocular cicatricial pemphigoid
Granulomatosis with polyangiitis	Optic neuritis
Graves' disease	Palindromic rheumatism (PR)
Guillain-Barre syndrome	PANDAS (Pediatric autoimmune neuropsychiatric disorders associated with streptococcus infections)
Hashimoto's thyroiditis	Paraneoplastic cerebellar degeneration (PCD)
Hemolytic anemia	Paroxysmal nocturnal hemoglobinuria (PNH)
Henoch-Schonlein purpura (HSP)	Pars planitis (peripheral uveitis)
Herpes gestationis or pemphigoid gestationis (PG)	Parsonage-Turner syndrome
Hidradenitis suppurativa (HS) (Acne inversa)	Pemphigus
IgA nephropathy	Peripheral neuropathy
IgG4-related sclerosing disease	Perivenous encephalomyelitis
Immune thrombocytopenic purpura (ITP)	Pernicious anemia (PA)
Inclusion body myositis (IBM)	POEMS syndrome
Interstitial cystitis (IC)	Polyarteritis nodosa
Juvenile arthritis	
Juvenile diabetes (Type 1 diabetes)	

Polyglandular syndromes type I, II, III	Scleritis
Polymyalgia rheumatica	Scleroderma
Polymyositis	Sjögren's Disease
Postmyocardial infarction syndrome	Stiff person syndrome (SPS)
Postpericardiectomy syndrome	Susac's syndrome
Primary biliary cholangitis	Sympathetic ophthalmia (SO)
Primary sclerosing cholangitis	Takayasu's arteritis
Progesterone dermatitis	Temporal arteritis/giant cell arteritis
Progressive hemifacial atrophy (PHA) Parry Romberg syndrome	Thrombocytopenic purpura (TTP)
Psoriasis	Thrombotic thrombocytopenic purpura (Ttp)
Psoriatic arthritis	Thyroid eye disease (Ted)
Pure red cell aplasia (PRCA)	Tolosa-Hunt syndrome (THS)
Pyoderma gangrenosum	Transverse myelitis
Raynaud's phenomenon	Type 1 diabetes
Reactive arthritis	Ulcerative colitis (UC)
Relapsing polychondritis	Undifferentiated connective tissue disease (UCTD)
Restless legs syndrome (RLS)	Uveitis
Retroperitoneal fibrosis	Vasculitis
Rheumatic fever	Vitiligo
Rheumatoid arthritis	Vogt-Koyanagi-Harada disease
Sarcoidosis	Warm autoimmune hemolytic anemia
Schmidt syndrome or Autoimmune polyendocrine syndrome type II	

## REFERENCES

Autoimmune Association. 2021. *Autoimmune disease list*. <https://autoimmune.org/disease-information> (accessed February 3, 2022).



## Appendix C

### Open Session Agendas

**Wednesday, November 18, 2020, 1:30 – 4:00 p.m. (ET)**

#### **Web Conference**

#### **Open Session Agenda**

- |             |   |
|-------------|---|
| 1:30 – 1:45 | Welcome and introductions<br><i>Bernard Rosof, M.D., Committee Chair, and Committee</i>   |
| 1:45 – 2:00 | Sponsor charge to the committee<br><i>Ellen Goldmuntz, M.D., Ph.D., Section Chief, Rheumatologic Autoimmune Disease Section, National Institute of Allergy and Infectious Diseases (NIAID), NIH</i> |
| 2:00 – 2:10 | Study background<br><i>Alex Keenan, Clerk, Subcommittee on Labor, Health and Human Services, Education and Related Agencies, Senate Committee on Appropriations (Minority Staff)</i>                |

2:10 – 2:25	Overview of NIH Institutes and Centers and funding structure <i>James McNamara, M.D., Section Chief, Autoimmunity and Mucosal Immunology Branch, Division of Allergy, Immunology and Transplantation, NIAID, NIH</i>
2:25 – 3:05	State of autoimmune diseases in the U.S. <i>Virginia Ladd, Founder, Past President Emerita, Advisor to the President, American Autoimmune Related Diseases Association</i>
3:05 – 3:45	Autoimmune disease research in the U.S. <i>Jane Buckner, M.D., President, Benaroya Research Institute at Virginia Mason</i>
3:45 – 4:00	Q & A
4:00	Adjourn

**Open Session**  
**February 1 – 2, 2021**  
**Full Schedule in Eastern Time**  
**Web Conference**

**Meeting Agenda<sup>1</sup>**

**February 1, 2021, 1:15 – 4:40p**

**OPEN SESSION**

1:15 – 1:30	<b>Open Session Begins</b>
1:30 – 1:45	Welcome and introductions <i>Bernard Rosof, M.D., Committee Chair and Committee</i>
1:45 – 2:10	NIH Extramural Grant Review Process – Center for Scientific Review (CSR) <i>Deborah Hodge, Ph.D., Scientific Review Officer, Division of Physiological and Pathological Sciences, CSR, NIH</i>

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<sup>1</sup> All presentations and slides for open sessions can be found at <https://www.nationalacademies.org/our-work/assessment-of-nih-research-on-autoimmune-diseases#sectionPastEvents>.

- 2:10 – 2:35 Advancing Women's Health Research at NIH  
*Lisa Begg, Dr.P.H., R.N.*, Senior Research Program Officer,  
Office of Research on Women's Health (ORWH), NIH
- 2:35 – 2:45 Break
- 2:45 – 2:55 Panel Discussion: NIH Autoimmune Research across ICs  
*Introductions – Committee Moderator*
- 2:55 – 3:10 *James McNamara, M.D.*, Section Chief, Autoimmunity  
and Mucosal Immunology Branch, Division of Allergy,  
Immunology and Transplantation, NIAID, NIH
- 3:10 – 3:25 *Marie Mancini, Ph.D.*, Program Director, Systemic  
Autoimmune Disease Biology Program, National Institute  
of Arthritis and Musculoskeletal and Skin Disease  
(NIAMS), NIH
- 3:25 – 3:40 *Ursula Utz, Ph.D.*, Program Director, Neuroimmunology,  
Autoimmunity, Neurovirology, Multiple Sclerosis, National  
Institute of Neurological Disorders and Stroke (NINDS),  
NIH
- 3:40 – 3:55 *Ruth Kirby*, Clinical Trials Specialist, National Heart, Lung,  
and Blood Institute (NHLBI), NIH
- 3:55 – 4:30 Discussion
- 4:30 Adjourn

**February 2, 2021, 1:00 – 3:15p**

### **OPEN SESSION**

- 1:00 – 1:05 Welcome and Introductions  
*Bernard Rosof, M.D.*, Committee Chair
- 1:05 – 1:30 Advances and Opportunities in Multiple Sclerosis  
*Nicholas LaRocca, Ph.D.*, Consultant, National Multiple  
Sclerosis Society (NMSS)

- 1:30 – 1:55     Advances and Opportunities in Autoimmune Arthritis  
*Emily von Scheven, M.D., M.A.S.*, Chief of Rheumatology,  
UCSF Benioff Children's Hospital  
*Mary K. Crow, M.D.*, Director, Autoimmunity and  
Inflammation Research Program; Co-Director, Mary  
Kirkland Center for Lupus Research at the HSS Research  
Institute
- 1:55 – 2:20     Advances and Opportunities in Type 1 Diabetes  
*Sanjoy Dutta, Ph.D.*, Vice President for Research, Juvenile  
Diabetes Research Foundation
- 2:20 – 2:45     Advances and Opportunities in Inflammatory Bowel  
Disease  
*Caren Heller, M.D., M.B.A.*, Chief Scientific Officer, Crohn's  
& Colitis Foundation
- 2:45 – 3:15     Discussions
- 3:15              Adjourn

**March 4 – 5, 2021**

**Public Session**

**Web Conference**

**Meeting Agenda**

**Thursday, March 4, 2021, 1:30 – 5:30 pm (EST)**

- 1:30              **Public Session Begins**
- 1:30 – 1:45     Welcome and introductions  
*Bernard Rosof, M.D.*, Committee Chair and Committee

**NIH Intramural Research for Autoimmune Diseases**

- 1:45 – 2:10    *Daniel Kastner, M.D., Ph.D.*, Scientific Director, Division of Intramural Research, NHGRI, NIH
- 2:10 – 2:35    *Karyl S. Barron, M.D.*, Deputy Director, Division of Intramural Research, NIAID, NIH
- 2:35 – 3:00    *Lisa G. Rider, M.D.*, Acting Head, Environmental Autoimmunity Group, Clinical Research Branch, NIEHS, NIH
- 3:00 – 3:25    *John O'Shea, Ph.D.*, Scientific Director and Director of Intramural Research Program, NIAMS, NIH
- 3:25 – 3:40    Break

**NIH Extramural Research for Autoimmune Diseases Across ICs**

- 3:40 – 4:05    *Lisa Spain, Ph.D.*, Program Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK, NIH
- 4:05 – 4:30    *Michael C. Humble, Ph.D.*, Program Administrator, Genes, Environment and Health Branch, Division of Extramural Research and Training, NIEHS, NIH
- 4:30 – 4:55    *Nishadi Rajapakse, Ph.D., M.H.S.*, Program Director, Transdisciplinary Collaborative Centers on Precision Medicine, Centers of Excellence on Environmental Health Disparities, Division of Scientific Programs, NIMHD, NIH
- 4:55 – 5:30    Discussion
- 5:30            Adjourn

**Friday, March 5, 2021, 1:00 – 3:15 pm (EST)**

1:00	<b>Public Session Begins</b>
1:00 – 1:05	Welcome and Introductions <i>Bernard Rosof, M.D., Committee Chair</i>
1:05 – 1:30	Advances and Opportunities in Lupus <i>Judith A. James, M.D., Ph.D.</i> , Vice President of Clinical Affairs, Member & Chair, Arthritis & Clinical Immunology, Oklahoma Medical Research Foundation; Associate Vice Provost for Clinical and Translational Science, Professor of Medicine, Professor of Pathology, Oklahoma University Health Sciences Center
1:30 -1:55	Advances and Opportunities in Dermatological Autoimmune Diseases <i>Victoria P. Werth, M.D.</i> , Professor of Dermatology at the Hospital of the University of Pennsylvania and the Veteran's Administration (V.A.) Medical Center; Chief, Dermatology, Philadelphia V.A. Hospital
1:55 – 2:20	Advances and Opportunities in Autoimmune Thyroid Diseases <i>Yaron Tomer M.D.</i> , Anita and Jack Saltz Chair in Diabetes Research Professor and Chair, Department of Medicine Albert Einstein College of Medicine, Montefiore Medical Center
2:20 – 2:45	Advances and Opportunities in Primary Biliary Cholangitis <i>Mark Pedersen, M.D.</i> , Assistant Professor of Medicine, Division of Digestive and Liver Disease, University of Texas Southwestern Medical Center
2:45 – 3:15	Discussion
3:15	Adjourn

## **Appendix D**

### **Epidemiology: Select Diseases**

#### **SJÖGREN'S DISEASE**

##### **Epidemiology Overview**

Few studies have examined the incidence or prevalence of Sjögren's disease, and the data are limited to "primary" Sjögren's disease (i.e., Sjögren's disease occurring alone), which excludes individuals with co-occurring systemic rheumatic disease such as SLE, rheumatoid arthritis, systemic sclerosis, or dermatomyositis. A recent study estimated the annual incidence of primary Sjögren's disease in New York County (Manhattan) as 3.5 cases per 100,000 persons (Izmirly et al., 2019). This estimate does not include children with Sjögren's disease and therefore grossly underestimates the overall incidence of Sjögren's disease. The same study estimated the prevalence of primary Sjögren's disease in this population to be 13.1 per 100,000 persons (Izmirly et al., 2019). Again, however, children were not included, and Sjögren's disease commonly co-occurs with other autoimmune diseases, so while this prevalence may reflect primary Sjögren's disease in adults, it fails to capture the full extent of individuals in the United States with Sjögren's disease. In recent studies, 30 percent of individuals with rheumatoid arthritis also had Sjögren's disease (Harrold et al., 2020), while about 15 to 20 percent of individuals with SLE had Sjögren's disease (Aggarwal et al., 2015; Baer et al., 2010). In addition, a study has shown that patients with primary Sjögren's disease are often initially misdiagnosed with SLE or rheumatoid arthritis (Rasmussen et

al., 2016). Thus, the overall prevalence of Sjögren's disease in the United States is likely greater than 0.3 percent of the population.

### **Sex, Age, Racial, and Ethnic Disparities**

Diagnosis of Sjögren's disease most commonly occurs in the fifth to seventh decades of life, though it may occur from early childhood through late adulthood (Brito-Zerón et al., 2020; Ramos-Casals et al., 2020; Sjögren's Foundation, 2021). Sjögren's disease is diagnosed more commonly in females, with a female-to-male ratio of 6:1 based on small studies in the United States (Izmirly et al., 2019; Maciel et al., 2017), though large global studies have found an even higher female-to-male ratio of 14:1 in adults and a slightly decreased ratio of 5:1 in children (Basiaga et al., 2020; Brito-Zerón et al., 2020; Ramos-Casals et al., 2020). Sjögren's disease occurs across races and ethnicities but is diagnosed more commonly in White individuals. Among over 10,000 adults with Sjögren's disease in a multinational study, 77 percent were White individuals, 14 percent Asian individuals, 6 percent Hispanic individuals, and 1.4 percent Black individuals (Brito-Zerón et al., 2020). Measures of disease activity indicated that disease activity was highest in Black individuals, followed by White, Asian, and Hispanic individuals.

Specific disease manifestations differed according to ethnicity and age (Ramos-Casals et al., 2021). For example, children had a higher frequency of glandular swelling, rashes, and cytopenias but a lower frequency of dryness, whereas the frequency of pulmonary and neuromuscular manifestations increased with age at presentation. In a recent U.S.-based study, the American Indian population was disproportionately affected by Sjögren's disease, displaying a higher risk of diagnosis and increased disease activity (Scofield et al., 2020). Additional studies are needed to further define racial and ethnic disparities.

## **SYSTEMIC LUPUS ERYTHEMATOSUS**

### **Epidemiology Overview**

A recent meta-analysis based on data from a Centers for Disease Control and Prevention (CDC) network of four national lupus registries estimated overall SLE incidence in the United States as 5.1 per 100,000 person years for 2002 to 2009 (Izmirly et al., 2021a).<sup>1</sup> Some of the most comprehensive data on SLE are from studies based in Michigan, Georgia, and California associated with the CDC national lupus registries. The

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<sup>1</sup>This study was published around the time the report was going into review.

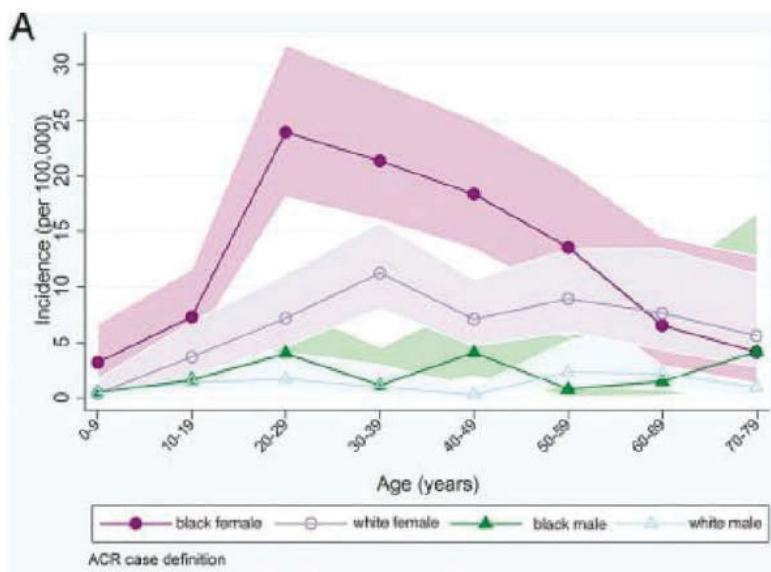
registries provide incidence and prevalence data for select state areas. Incidence of SLE was 4.6 per 100,000 persons in San Francisco County in California (Dall'Era et al., 2017), 5.5 per 100,000 in southeastern Michigan (Somers et al., 2014), and 5.6 per 100,000 in Fulton and DeKalb counties in Georgia (Lim et al., 2014). The Manhattan Lupus Surveillance Program (Izmirly et al., 2017), a registry of residents in New York County (Manhattan), found an annual incidence of 4.6 cases per 100,000 persons for 2007 to 2009 and a prevalence rate of 62.2 cases per 100,000 persons for the year 2007.

### Sex, Age, Racial and Ethnic Disparities

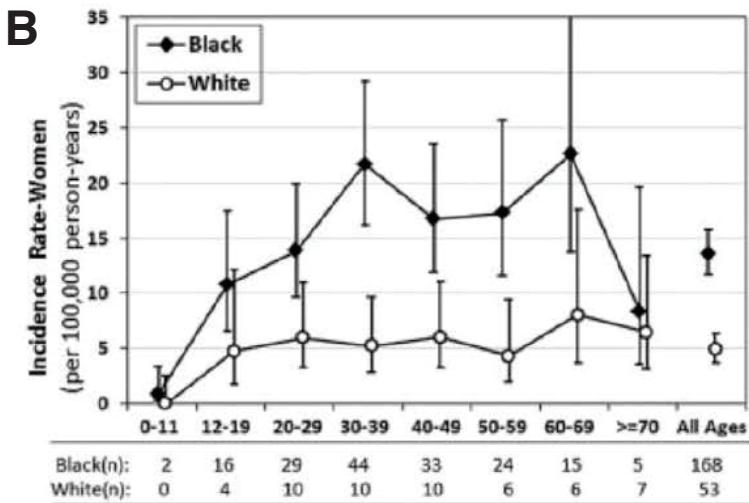
A meta-analysis of CDC national lupus registries found the U.S. incidence of SLE in women to be approximately seven times higher than in men for the years 2002–2009 (Izmirly et al., 2021a). In each of the Michigan (Figure D-1A), Georgia, and California studies, incidence rates for women were 5 to 10 times higher than for men across all ages and in each racial or ethnic group studied (Dall'Era et al., 2017; Lim et al., 2014; Somers et al., 2014). For women, each of these studies also found considerably higher rates of the disease in Black patients than in White patients, with a marked increase in incidence between the ages of 20 and 60 years, as represented by Georgia data in Figure D-1B. For White, Asian-Pacific Islander, and Hispanic patients, however, incidence rates among women showed less variation across these age groups (Figure D-1C).

Similarly, in the New York study (Izmirly et al., 2017), the incidence and prevalence rates of SLE were around nine times higher in women than in men. When examining only women, incidence and prevalence rates were highest for non-Hispanic Black women, and showed a marked increase in the 20–59 age groups (Figure D-2). White, Hispanic, and Asian women showed less variation across these age groups.

Investigators have conducted a meta-analysis of data from the California, Georgia, Michigan, and New York studies and from the Indian Health Service and estimated a prevalence of SLE for the United States of 72.8 per 100,000 (Izmirly et al., 2021b). Between 80 and 90 percent of individuals with SLE are female, and SLE is two to three times more common in Black, Indigenous, and people of color. The highest prevalence of SLE was seen in American Indian and Alaska Native women at 270.6 per 100,000 women, and Black women at 230.9 per 100,000 women, while the rate for Hispanic women was lower at 120.7 per 100,000 women but still 43 percent higher than the rate for White women (84.7 per 100,000 women) and Asian and Pacific Islander women (84.4 per 100,000 women) (Izmirly et al., 2021b).

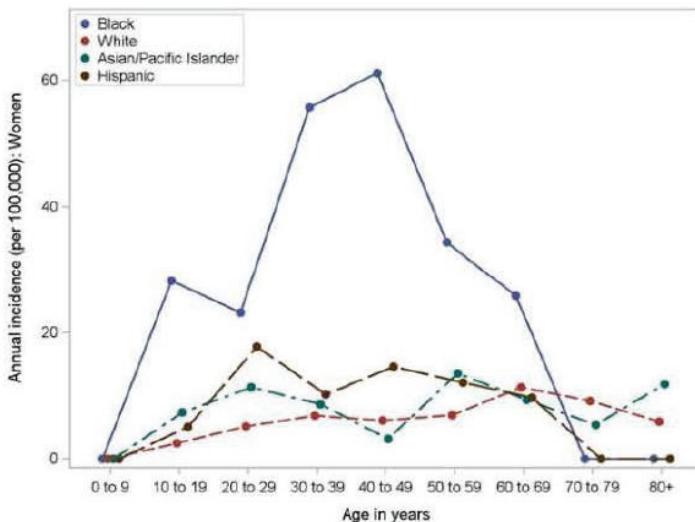


Incidence of Systemic Lupus Erythematosus in Men and Women in southeastern Michigan, 2002–2004 by age, sex, and race. Somers et al., 2014.



Incidence of Systemic Lupus Erythematosus in Women in Fulton and DeKalb Counties, Georgia, 2002–2004 by age and race. Lim et al., 2019.

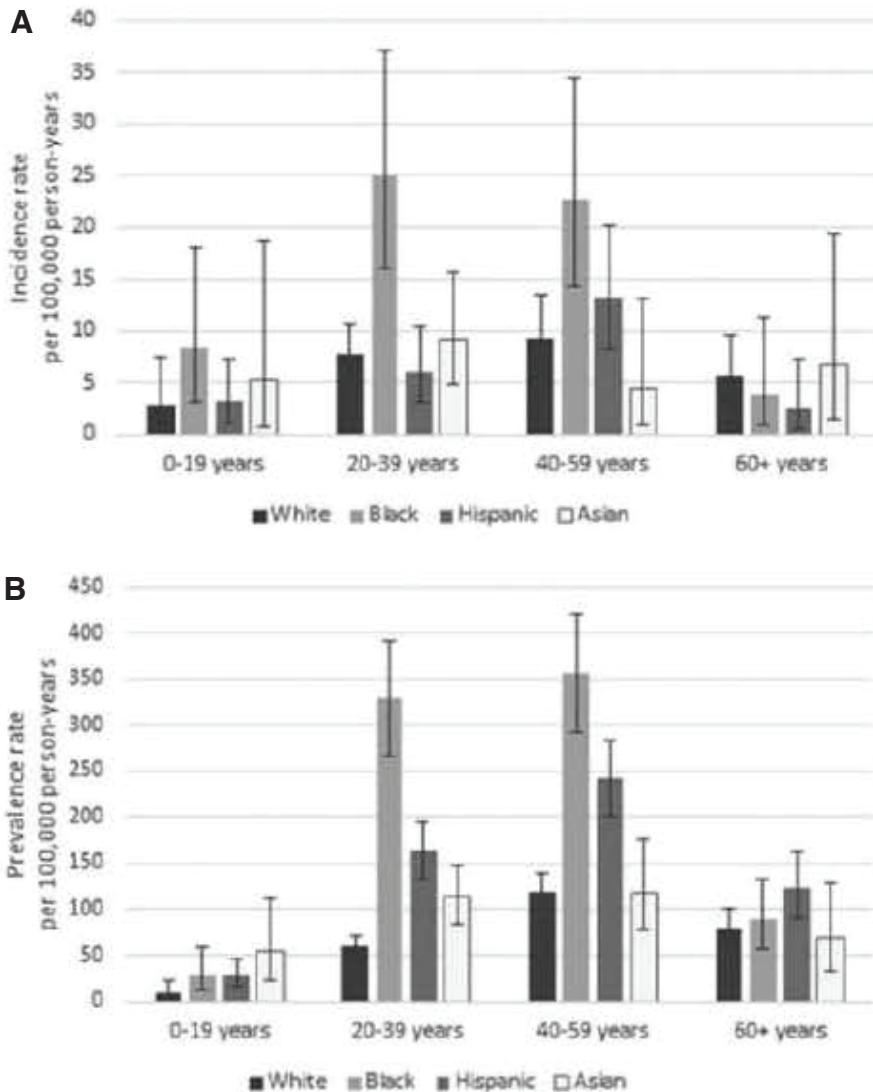
**FIGURE D-1** Figure A shows differences in the incidence of SLE in males and females in Michigan; Figures A, B, and C show differences between racial and ethnic groups in Michigan, Georgia, and California, respectively.  
 SOURCES: Dall'Era et al., 2017; Lim et al., 2014; Somers et al., 2014.

**C**

Incidence of Systemic Lupus Erythematosus in Women in San Francisco County, California, 2007–2009, by age and race-ethnicity. Dall’Era et al., 2017.

**FIGURE D-1** Continued

Although the rates of some autoimmune diseases are lower in children than adults, these diseases have a significant impact on the children and their families. Juvenile-onset SLE, which occurs before age 18, is estimated to affect about 15 to 20 percent of people with SLE (Charras et al., 2021; Hersh et al., 2010). Data on U.S. studies suggest that the incidence of juvenile SLE ranges from 0.36 to 2.5 per 100,000 children and the estimated prevalence is from 1.9 to 34.1 per 100,000 children (Charras et al., 2021). Childhood-onset SLE shows population-level differences in incidence and prevalence similar to those seen in adult-onset disease. In a study of the U.S. Medicaid beneficiary population from 2000 to 2004, the annual incidence of SLE in children 3 to <18 years old was 2.22 per 100,000 Medicaid-enrolled children and that of lupus nephritis, a frequent complication of SLE, was 0.72 per 100,000 (Hiraki et al., 2012). In the same population, prevalence estimates for children with SLE were 9.73 per 100,000 Medicaid enrolled children, of whom 84 percent were female, 40 percent were Black, 25 percent were Hispanic, and 21 percent were White. In addition, 37 percent of children with SLE had lupus nephritis, representing a prevalence of 3.64 per 100,000 Medicaid-enrolled children. Both prevalence and incidence rates of SLE and lupus nephritis increased with age, were higher in girls than in boys, and were higher in all non-White racial and ethnic groups (Hiraki et al., 2012).



**FIGURE D-2** Incidence and prevalence of SLE in women residents of New York County (Manhattan), showing age and race and ethnicity. Figure A shows incidence during 2007–2009, and Figure B shows prevalence during 2007.

SOURCE: Izmirly et al., 2017.

SLE exemplifies important disparities in disease severity, physical and mental morbidity, and mortality across racial and ethnic groups. Indeed, SLE is the fifth leading cause of death in Black and Hispanic females aged 15 to 24 years old in the United States (Yen and Singh, 2018). Furthermore, research has identified disparities in outcomes of SLE in children, including care delivery and SLE-related conditions such as mental health disorders (Rubinstein and Knight, 2020). These disparities may exist according to race and ethnicity, income, and geography.

Some of the most severe SLE manifestations are lupus nephritis and neuropsychiatric lupus (NPSLE). Although lupus nephritis and NPSLE typically occur early in the disease course, they can occur years after the onset of disease in some patients. NPSLE has many manifestations, including seizures, cerebrovascular disease, demyelinating syndrome, psychosis, cognitive dysfunction, acute confusional state, chorea, myopathy, mononeuritis multiplex, and peripheral neuropathies (Ford et al., 1999; Gulinello et al., 2012). Both nephritis and NPSLE manifestations may remit, or more commonly, result in long-standing damage.

One U.S. study of end-stage renal disease (ESRD) resulting from SLE found that rates of ESRD in Black individuals ages 5 to 39 with lupus nephritis increased during the 1995 to 2006 period (Costenbader et al., 2011). Researchers, using data from the same study, further observed that Black children were half as likely to receive a kidney transplant as White children and twice as likely to die from ESRD caused by lupus nephritis. Hispanic children and adults, compared with non-Hispanic children and adults, were also less likely to receive kidney transplants. Researchers also found that children living in the U.S. West and Northwest were placed on kidney transplant wait lists more often than children living in the South (Hiraki et al., 2011). A large study of hospitalized children with SLE in the United States, using data from the Kids' Inpatient Database,<sup>2</sup> found both regional and racial disparities in mortality, with Black children and children from southern states having twice the risk of death compared with White children and children from northeastern states (Knight et al., 2014). While these studies do reveal disparities among certain U.S. subpopulations, the committee believes that efforts to understand these disparities would benefit from large epidemiologic studies covering a wide range of demographic characteristics.

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<sup>2</sup> Additional information is available at <https://www.hcup-us.ahrq.gov/kidoview.jsp>.

## ANTIPHOSPHOLIPID SYNDROME

### Epidemiology Overview

Because of technical differences in assessing antiphospholipid antibodies and APS's overlap with SLE and other autoimmune diseases, epidemiology data for this illness are scarce, but the prevalence is thought to be 40 to 50 cases per 100,000 persons (Cervera, 2017; Duarte-Garcia et al., 2019). Reports on demographics, incidence, prevalence, and population outcome often come from retrospective studies that are not generalizable (Erkan et al., 2012, 2021). A recent population-based study in Minnesota addresses that bias, but is limited in its generalizability in that it is based in a relatively small and homogenous population with a low incidence of SLE (Duarte-Garcia et al., 2019). Prospective studies and clinical trials with diverse participants and large sample sizes could yield more accurate and relevant results (Erkan et al., 2012; FDA, 2021).

The 2022 *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) code for antiphospholipid syndrome (D68.61) became effective on October 1, 2021 (ICD10 Data, 2021). This code excludes the common finding of a positive lupus inhibitor test, as measured by specialized coagulation tests, in an asymptomatic person, suggesting use of the code R76.02 instead.

### Sex, Age, Racial and Ethnic Disparities

Isolated thrombotic APS affects both sexes equally (NORD, 2016). When APS occurs with another autoimmune disease, that disease is most often lupus, and because the majority of individuals with lupus are female, APS associated with other illnesses is female predominant. Considering obstetric and thrombotic APS together, APS is female predominant. In a population-based study of incidence of APS in ages  $\geq 18$  years, the female-to-male ratio was 1.0 (Duarte-Garcia et al., 2019); this low ratio may result from the relative lack of representation of people at higher risk of SLE in this study. Unlike SLE, the risk of APS is greatest in White populations and relatively low in Black populations (Duarte-García et al., 2019; Izmirly et al., 2021b).

## RHEUMATOID ARTHRITIS

### Epidemiology Overview

Rheumatoid arthritis is one of the most common autoimmune diseases, affecting an estimated 2.4 million adults in the United States

(Kawatkar et al., 2019). Although incidence rates for rheumatoid arthritis decreased in the United States and Europe in the latter part of the 20th century, the trends since the 1990s have demonstrated relatively stable or somewhat rising rates (Myasoedova et al., 2010; Safiri et al., 2019). During the period 1995 to 2007, based on the Olmsted County, MN, population, overall age- and sex-adjusted annual incidence was 40.9 per 100,000 population (Myasoedova et al., 2010).

### **Sex, Age, Racial and Ethnic Disparities**

The incidence of rheumatoid arthritis begins to rise in women and men aged 35 to 54, with the highest rates in both women and men among those aged 65 to 74. Female-to-male incidence ratios are about 3:1 during reproductive and perimenopausal years, and decrease to about 1.5:1 for individuals over the age of 55 (Myasoedova et al., 2010). Incidence is higher in the United States and northern European countries (Alamanos et al., 2006). Studies in specific American Indian and Alaska Native communities (Blackfeet, Yakima, Chippewa, and Pima) have reported higher prevalence rates of rheumatoid arthritis than reported for the general U.S. population estimate (Kawatkar et al., 2019; McDougall et al., 2017).

With respect to health outcomes and disability measures among people with rheumatoid arthritis, studies have observed higher disease activity and lower rates of remission among Black and Hispanic populations compared with White populations (Barton et al., 2011; Greenberg et al., 2013). Early treatment with the newer, more targeted therapies is recommended (Fraenkel et al., 2021), but use of these medications may depend on insurance coverage and access to care.

## **PSORIASIS**

### **Epidemiology Overview**

The annual incidence of psoriasis in the United States is estimated to be 78.9 new cases per 100,000 persons (Icen et al., 2009), though a more recent study based on health administrative data for Ontario, Canada, reported an incidence rate of 69.9 cases per 100,000 persons in 2015 (Eder et al., 2019). A medical records-based study in a large health maintenance organization in northern California estimated the prevalence of psoriasis to be 939 per 100,000, which translates to approximately 2.5 million U.S. adults (Asgari et al., 2013). The prevalence among U.S. children is lower, with 128 cases per 100,000 (Paller et al., 2018).

### **Sex, Age, Racial and Ethnic Disparities**

The incidence of psoriasis is similar among men and women; however men may experience more severe forms of the disease (Hägg et al., 2013). The prevalence of psoriasis increases over the life course, with prevalence of 0.12 percent at age 1 year and 1.2 percent at age 18 years (Augustin et al., 2010). A 2015 study of psoriasis in U.S. children and adolescents estimated the prevalence at 128 per 100,000 persons. The prevalence was higher in females than in males—146 per 100,000 versus 110 per 100,000—and increased with age, ranging from 30 per 100,000 in the 0 to 3 age group to 205 per 100,000 in the 12 to 17 age group (Paller et al., 2018). The location of lesions and the type of psoriasis may also vary by age. For example, psoriasis is more likely to affect the face in children, and guttate psoriasis, which manifests as red, scaly, small, teardrop-shaped spots, is more common among children than adults (Boehncke and Schön, 2015).

White individuals had the highest prevalence of psoriasis at 3.6 percent, followed by other racial/ethnic groups (including multiracial) at 3.1 percent, and Hispanic and Black individuals at 1.9 percent and 1.5 percent, respectively (Armstrong et al., 2021).

## **INFLAMMATORY BOWEL DISEASE**

### **Epidemiology Overview**

Ulcerative colitis and Crohn's disease have emerged as global diseases in the 21st century (Ananthakrishnan et al., 2020). Estimates of the prevalence of these diseases in the United States, obtained using U.S. medical records, range from 1.3 to 2.3 million persons. Another study using less rigorous, self-report methods suggest estimates as high as 3.9 million persons. The true prevalence is unknown (see Box 2-1 in Chapter 2).

### **Sex, Age, Racial and Ethnic Disparities**

Epidemiologic studies from Olmsted County, MN, found that the incidence of Crohn's disease among women and men was about the same, though the incidence of ulcerative colitis was slightly higher for males than females (Shivashankar et al., 2017). The highest incidence of both ulcerative colitis and Crohn's disease occurs in the second to fourth decades, and particularly in the 20 to 29 age range.

Pediatric IBD accounts for approximately 25 percent of cases of IBD, and approximately 18 percent of children with IBD will present before age 10 (Rosen et al., 2015). The prevalence of IBD in children under 17 years of age is about 77.0 per 100,000 people in the United States, which

translates into 58,000 children between the ages of 2 and 17 affected by IBD (Ye et al., 2020). The prevalence of pediatric IBD in the United States has increased by 133 percent from 2007 to 2016, from 33.0 to 77.0 cases per 100,000 people, with Crohn's disease being twice as prevalent as ulcerative colitis at 45.9 cases of Crohn's disease per 100,000 children versus 21.6 cases of ulcerative colitis per 100,000 children (Ye et al., 2020). Studies have observed geographic variability in IBD rates, with the incidence rising in developing countries and urban areas. Changes in diet that affect the intestinal microbiota, exposure to sunlight or temperature differences, socioeconomic status, and hygiene are among the environmental variables that most likely explain that geographic variability (Benchimol et al., 2017; Bernstein et al., 2019). In infantile IBD or very-early-onset IBD, researchers have identified genetic mutations as the basis for this susceptibility in up to 10 percent of cases, which suggests a simple monogenic origin of the disease in these cases (Ouahed, 2021).

White individuals and people of Ashkenazi Jewish descent have the highest incidence of IBD, though the incidence of IBD is increasing in Hispanic and Asian populations (Hou et al., 2009; Santos et al., 2018). IBD is more prevalent in urban areas and higher socioeconomic populations compared with rural areas and lower socioeconomic populations (Benchimol et al., 2017; Bernstein et al., 2019). IBD is a familial disorder in up to 12 percent of those affected, and the strongest risk factor for the development of IBD is a first-degree relative with the disease. There is an approximately 4-fold increased risk of ulcerative colitis in the children of mothers or fathers with ulcerative colitis and an almost 8-fold increased risk of Crohn's disease in the children of mothers or fathers with Crohn's disease (Agrawal et al., 2021; Moller et al., 2015), as well as similar patterns regarding which parts of the intestinal system the disease affects. Some children of parents with IBD develop disease during the first decade of life. In a small study, the relative risk for concordant disease in monozygotic twins was estimated at 95.4 for Crohn's disease and 49.5 for ulcerative colitis. The relative risk in dizygotic twins was 42.2 and 0.0 for Crohn's disease and ulcerative colitis, respectively (Bengtson et al., 2010).

## CELIAC DISEASE

### Epidemiology Overview

Celiac disease is characterized by the presence of tissue transglutaminase autoantibodies (tTGA) that often precedes the biopsy-proven diagnosis of celiac disease (Gandini et al., 2021). Using the presence of tTGA in serum samples to provide an estimate of disease in the United States, a study based on data from the National Health and Nutrition

Examination Survey estimated a seroprevalence of 790 per 100,000 persons over 5 years of age (Mardini et al., 2015), which corresponds to 2.3 million people. Estimates place the worldwide seroprevalence of celiac disease at 1.4 percent, and the worldwide prevalence of biopsy-proven celiac disease at 0.7 percent (Singh et al., 2018).

### **Sex, Age, Racial and Ethnic Disparities**

Celiac disease is 1.5 times more common in females than in males, and approximately 2 times more common in children than in adults (Singh et al., 2018). The prevalence and incidence of celiac disease has been increasing over time, which suggests that changing environmental factors are influencing the development of this disease (Lohi et al., 2007; Ludvigsson et al., 2013). Studies have found the prevalence of celiac disease to be highest in Europe and Oceania (0.8 percent) and lowest in South America (0.4 percent), with Africa (0.5 percent), North America (0.5 percent), and Asia (0.6 percent) being intermediate (Singh et al., 2018). Studies estimate that the prevalence of celiac disease in the United States is four to eight times higher among non-Hispanic Whites compared with other racial and ethnic groups (Mardini et al., 2015).

## **PRIMARY BILIARY CHOLANGITIS**

### **Epidemiology Overview**

The incidence of PBC in the United States is 4 to 5 per 100,000 persons per year (Lu et al., 2018). Incidence rates have been relatively stable during the past 20 years (Kanth et al., 2017; Lu et al., 2018), but the prevalence has increased during this time from approximately 22 per 100,000 persons to 39 per 100,000 persons (Lu et al., 2018). This difference may reflect earlier treatment leading to improved patient outcomes. The 5-year mortality rate is approximately 15 to 20 percent.

### **Sex, Age, Racial and Ethnic Disparities**

PBC is predominantly a disorder of women, who account for approximately 90 percent of all cases. The typical age of onset is in the fifth or sixth decades of life, and the highest reported incidence and prevalence is in northern Europe and the northern United States (Lv et al., 2021).

Studies have reported increased prevalence in some Indigenous groups in the United States and Canada (Yoshida et al., 2006). In comparison to White patients with PBC, Indigenous Canadians present with advanced disease and have worse long-term outcomes (Roberts et al.,

2022). Although rates are higher among White and Asian and Pacific Islanders compared with Black populations (Lu et al., 2018), the severity of disease at diagnosis may be greater in Black and Hispanic compared with White populations (Peters et al., 2007), which has implications for treatment options and outcomes.

## MULTIPLE SCLEROSIS

### Epidemiology Overview

Multiple sclerosis is the most common CNS inflammatory disorder, though incidence data for the United States do not exist. The overall 2010 U.S. prevalence of multiple sclerosis was estimated at 309 per 100,000 persons (Wallin et al., 2019), equating to approximately 775,000 cases of multiple sclerosis in the United States in 2020. The prevalence of multiple sclerosis has increased worldwide between 1990 and 2016 (Walton et al., 2020), while studies have not consistently found an increase in incidence. Therefore, the increasing multiple sclerosis prevalence is likely a result of a combination of increased awareness leading to increased detection, better diagnostic technology, the increasing age of the populations studied, and increased survival of those with the disease.

### Sex, Age, Racial and Ethnic Disparities

Women are more than twice as likely as males to live with multiple sclerosis as males, with a 2.8-fold higher prevalence (Wallin et al., 2019). For adult-onset multiple sclerosis, the mean age at clinical diagnosis is 30 years (Mayo Clinic, 2021). Onset of multiple sclerosis in childhood is uncommon, occurring in 2 to 10 percent of individuals with multiple sclerosis (Yan et al., 2020; Yeh et al., 2009). Sex and age at diagnosis differ by the type of multiple sclerosis, however, with nearly equal proportions of men and women having primary progressive multiple sclerosis and showing a later onset—approximately 10 years—than those with relapsing-remitting multiple sclerosis (Tremlett et al., 2005, Table 2, p. 1921).

A study of racial and ethnic variability in multiple sclerosis in the multi-ethnic community-dwelling members of a California health plan showed a higher annual incidence in Black members, with 10.2 cases per 100,000 persons, compared with White members, with 6.9 cases per 100,000 persons, and lower rates in Hispanic members, with 2.9 cases per 100,000 persons, and Asian and Pacific Islander members, with 1.4 cases per 100,000 persons (Langer-Gould et al., 2013). The prevalence of multiple sclerosis is higher in non-Hispanic Black compared with non-Hispanic White populations, and there is even lower prevalence in Asian,

Pacific Islander, and Hispanic populations (Romanelli et al., 2020). There is a dearth of data on delay in diagnosis in racial and ethnic minority populations, however, with several studies suggesting that delays result from a lack of access to a multiple sclerosis specialist and to perceptions among physicians that the disease is more common in White populations (Stuifbergen et al., 2021).

## TYPE 1 DIABETES

### Epidemiology Overview

A study in Olmstead County, MN, between 1994 and 2010 reported an overall annual incidence of type 1 diabetes of 9.2 per 100,000 people per year among all ages, and 19.9 per 100,000 people for those younger than 20 years (Cartee et al., 2016). A population-based registry across five U.S. sites reported an annual incidence of 21.7 per 100,000 in people under the age of 20 in 2011 to 2012 (Mayer-Davis et al., 2017).

An estimated 178,000 individuals under the age of 20 have type 1 diabetes in the United States (Dabelea et al., 2014). One study based on non-verified, self-reported data collected through the National Health Interview Study in 2016 and 2017 estimated that 0.5 percent of the U.S. population had a diagnosis of type 1 diabetes. In 2020, this would have represented about 1,485,000 adults living with the disease (Bullard et al., 2018; Xu et al., 2018).

### Sex, Age, Racial and Ethnic Disparities

The annual incidence of type 1 diabetes in individuals 19 years and younger is almost twice that of adults 20 to 64 years of age (Rogers et al., 2017). In studies of individuals ages 0 to 19, type 1 diabetes often occurs during two peaks: at ages 5 to 7 and during puberty (Atkinson et al., 2014). In the 0 to 19 age group, the prevalence of type 1 diabetes is similar in males and females (Dabelea et al., 2014), though the incidence of the disease increased among boys but not among girls between 2002 and 2012 (Mayer-Davis et al., 2017). In adults, there is a higher incidence of type 1 diabetes in males compared with females (Rogers et al., 2017).

During the period from 2001 to 2009, a large U.S. study showed an increase in type 1 diabetes prevalence in the 0–19 age group from 1.48 per 1,000 individuals to 1.93 per 1,000 individuals (Dabelea et al., 2014). A subsequent study of the U.S. Medicaid pediatric population showed an increase in annual type 1 diabetes prevalence from 1.29 per 1,000 individuals to 2.34 per 1,000 individuals during 2002 to 2016 (Chen et al.,

2019). This trend was not seen, however, in a study spanning 1994 to 2010 in Olmsted County, MN (Cartee et al., 2016).

In the United States, the prevalence of type 1 diabetes in the age 0 to 19 population is highest among non-Hispanic White persons compared with Hispanic, African American, American Indian, and Native Alaskan persons (Dabelea et al., 2014). The incidence of type 1 diabetes in that age group increased 1.4 percent annually, from 19.5 cases per 100,000 youths per year in 2002 and 2003 to 21.7 cases per 100,000 youths per year in 2011 and 2012. There was a greater rate of increase among Hispanic persons compared with non-Hispanic White persons, with a 4.2 percent annual increase among Hispanic individuals versus a 1.2 percent annual increase in non-Hispanic White individuals (Mayer-Davis et al., 2017), suggesting the influence of environmental factors that may differentially influence risk in different ethnic and racial groups.

## AUTOIMMUNE THYROID DISEASES

### Epidemiology Overview

Despite being among the most common autoimmune disorders (Bülow Pedersen and Laurberg, 2009), there is a lack of detailed epidemiologic data on Hashimoto's thyroiditis and Graves' disease for the past 20 years for the United States. Historically, data from Rochester, MN, have served as a key source for U.S. data on autoimmune thyroid diseases (Furszyfer et al., 1972), although these data predated current methods for thyroid function testing. Nonetheless, an important finding based on the Rochester data from 1935 to 1967 was documenting a sharp rise in incidence over the three decades, an increase that appeared most pronounced among those younger than 40 years old. Data in males were too sparse to characterize temporal trends, and the study did not find evidence of a cohort effect.

European annual incidence estimates of autoimmune thyroid disease have varied widely, from 51 to 490 cases per 100,000 persons (Gallofré et al., 1994; Vanderpump et al., 1995). Differences in methodologies and nomenclature across studies likely contribute to the wide range of estimates, although true regional variation should not be ruled out. A study in 2008 to 2013 in Sheffield, United Kingdom, reported an annual incidence of 24.8 cases per 100,000 persons, with a median age of 44 years old at diagnosis. Women accounted for 80 percent of those affected (Hussain et al., 2017). A large cohort study in the Netherlands examined thyroid medication use and thyroid hormone levels to classify overt and subclinical thyroid diseases. Thyroid medication was used by 3.1 percent of participants, the majority (98.2 percent) of whom used levothyroxine.

Subclinical hypothyroidism was detected in 9.4 percent of the people who were not taking thyroid medications (Wouters et al., 2020).

### Sex, Age, Racial and Ethnic Disparities

Onset of autoimmune thyroid diseases typically occurs in mid- to late-adulthood (Cooper and Stroehla, 2003). A strong female preponderance of up to 95 percent has been reported (Cooper and Stroehla, 2003); epidemiologic data are lacking for males as a result of how rare thyroid disease is in men. U.S. data indicate that the prevalence of Hashimoto's thyroiditis is highest in White populations. A histologic study in Baltimore from 1955 to 1960 documented an approximately four times greater prevalence in White females compared with Black females (Masi, 1965), and a study based on data from the third National Health and Nutrition Examination Survey conducted from 1988 to 1994 found that prevalence of anti-thyroid antibodies was highest among White populations, followed by Mexican American populations, and was lowest in Black populations (Hollowell et al., 2002). Trends related to race and ethnicity have been less well characterized for Graves' disease. However, a 2014 report of active-duty U.S. military personnel found that the incidence of Graves' disease was significantly higher among individuals from Black and Asian or Pacific Islander populations compared with those from White populations, and trended higher in Hispanic populations compared with White populations (McLeod et al., 2014). This study also corroborated the earlier race and ethnicity trends observed for Hashimoto's thyroiditis (McLeod et al., 2014).

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## Appendix E

### Mission Statements of NIH's Institutes and Centers

IC Name	IC Mission
National Cancer Institute (NCI)	The National Cancer Institute (NCI) leads, conducts, and supports cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives (NCI, 2018).
National Eye Institute (NEI)	The mission of the National Eye Institute (NEI) is to eliminate vision loss and improve quality of life through vision research. To achieve this mission, NEI provides leadership to drive innovative research to understand the eye and visual system, prevent and treat vision diseases, and expand opportunities for people who are blind or require vision rehabilitation; foster collaboration in vision research and clinical care to develop new ideas and share knowledge across other fields; recruit, inspire, and train a talented and diverse new generation of individuals to expand and strengthen the vision workforce; educate health care providers, scientists, policymakers, and the public about advances in vision research and their impact on health and quality of life (NEI, 2021).
National Heart, Lung, and Blood Institute (NHLBI)	The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood disorders and enhance the health of all individuals so that they can live longer and more fulfilling lives (NHLBI, 2014).

IC Name	IC Mission
National Human Genome Research Institute (NHGRI)	As a leading authority in the field of genomics, the mission of the National Human Genome Research Institute (NHGRI) is to accelerate scientific and medical breakthroughs that improve human health. NHGRI does this by driving cutting-edge research, developing new technologies, and studying the impact of genomics on society (NHGRI, 2018).
National Institute on Aging (NIA)	The mission of the National Institute on Aging (NIA) is to support and conduct genetic, biological, clinical, behavioral, social, and economic research on aging; foster the development of research and clinician scientists in aging; provide research resources, and disseminate information about aging and advances in research to the public, health care professionals, and the scientific community, among a variety of audiences (NIA, 2021).
National Institute on Alcohol Abuse and Alcoholism (NIAAA)	The mission of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) is to generate and disseminate fundamental knowledge about the effects of alcohol on health and well-being, and apply that knowledge to improve diagnosis, prevention, and treatment of alcohol-related problems, including alcohol use disorder, across the lifespan (NIAAA, 2021).
National Institute of Allergy and Infectious Diseases (NIAID)	The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. For more than 60 years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world (NIAID, 2021).
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)	The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of basic and clinical scientists to carry out this research; and the dissemination of information on research progress in these diseases (NIAMS, 2021).
National Institute of Biomedical Imaging and Bioengineering (NIBIB)	The mission of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) is to improve health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating engineering and physical sciences with biology and medicine to advance our understanding of disease and its prevention, detection, diagnosis, and treatment. NIBIB supports emerging technology research and development within its internal laboratories and through grants, collaborations, and training (NIBIB, 2021).

IC Name	IC Mission
<i>Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)</i>	The mission of the <i>Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)</i> is to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all (NICHD, 2019).
<i>National Institute on Deafness and Other Communication Disorders (NIDCD)</i>	Established in 1988, the <i>National Institute on Deafness and Other Communication Disorders (NIDCD)</i> is mandated to conduct and support biomedical and behavioral research and research training in the normal and disordered processes of hearing, balance, taste, smell, voice, speech, and language. The institute also conducts and supports research and research training related to disease prevention and health promotion; addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders; and supports efforts to create devices that assist individuals with hearing loss or other communication disorders (NIDCD, 2019).
<i>National Institute of Dental and Craniofacial Research (NIDCR)</i>	The mission of the <i>National Institute of Dental and Craniofacial Research (NIDCR)</i> is to advance fundamental knowledge about dental, oral, and craniofacial (DOC) health and disease and translate these findings into prevention, early detection, and treatment strategies that improve overall health for all individuals and communities across the lifespan (NIDCR, 2018).
<i>National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)</i>	The mission of the <i>National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)</i> is to conduct and support medical research and research training and to disseminate science-based information on diabetes and other endocrine and metabolic diseases; digestive diseases, nutritional disorders, and obesity; and kidney, urologic, and hematologic diseases, to improve people's health and quality of life (NIDDK, 2021).
<i>National Institute on Drug Abuse (NIDA)</i>	The mission of <i>National Institute on Drug Abuse (NIDA)</i> is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health (NIDA, 2021).
<i>National Institute of Environmental Health Sciences (NIEHS)</i>	The mission of the <i>National Institute of Environmental Health Sciences (NIEHS)</i> is to discover how the environment affects people in order to promote healthier lives (NIEHS, 2019).

IC Name	IC Mission
National Institute of General Medical Sciences (NIGMS)	The National Institute of General Medical Sciences (NIGMS) supports basic research that increases our understanding of biological processes and lays the foundation for advances in disease diagnosis, treatment, and prevention. NIGMS-funded scientists investigate how living systems work at a range of levels from molecules and cells to tissues and organs, in research organisms, humans, and populations. Additionally, to ensure the vitality and continued productivity of the research enterprise, NIGMS provides leadership in training the next generation of scientists, in enhancing the diversity of the scientific workforce, and in developing research capacity throughout the country (NIGMS, 2021).
National Institute of Mental Health (NIMH)	The mission of the National Institute of Mental Health (NIMH) is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure (NIMH, 2021).
National Institute on Minority Health and Health Disparities (NIMHD)	The mission of the National Institute on Minority Health and Health Disparities (NIMHD) is to lead scientific research to improve minority health and reduce health disparities. To accomplish this, NIMHD plans, coordinates, reviews, and evaluates NIH minority health and health disparities research and activities; conducts and supports research in minority health and health disparities; promotes and supports the training of a diverse research workforce; translates and disseminates research information; and fosters innovative collaborations and partnerships (NIMHD, 2021).
National Institute of Neurological Disorders and Stroke (NINDS)	The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease for all people. To support this mission, NINDS supports and performs basic, translational, and clinical neuroscience research through grants-in-aid, contracts, scientific meetings, and through research in its own laboratories, and clinics; funds and conducts research training and career development programs to increase basic, translational and clinical neuroscience expertise and ensure a vibrant, talented, and diverse work force; promotes the timely dissemination of scientific discoveries and their implications for neurological health to the public, health professionals, researchers, and policy-makers (NINDS, 2021).
National Institute of Nursing Research (NINR)	The mission of the National Institute of Nursing Research (NINR) is to promote and improve the health of individuals, families, and communities. To achieve this mission, NINR supports and conducts clinical and basic research and research training on health and illness, research that spans and integrates the behavioral and biological sciences, and that develops the scientific basis for clinical practice (NIH, 2020).

<b>IC Name</b>	<b>IC Mission</b>
National Library of Medicine (NLM)	The National Library of Medicine (NLM) collects, organizes, and makes available biomedical science information to scientists, health professionals, and the public. The Library's Web-based databases, including PubMed/Medline and MedlinePlus, are used extensively around the world. NLM conducts and supports research in biomedical communications; creates information resources for molecular biology, biotechnology, toxicology, and environmental health; and provides grant and contract support for training, medical library resources, and biomedical informatics and communications research (NIH, 2019).
NIH Clinical Center (CC)	The NIH Clinical Center (CC) provides hope through pioneering clinical research to improve human health (NIH Clinical Center, 2020).
Center for Information Technology (CIT)	The Center for Information Technology (CIT) provides the NIH community with a secure and reliable IT infrastructure and a variety of IT and scientific computing services that support its mission-critical research and administrative activities. Among its activities, CIT provides a robust and secure enterprise network service for NIH staff; state-of-the-art, high-performance scientific computing platforms and applications; secure access to IT systems, including computers and applications; data-processing, hosting, and storage facilities; cloud computing infrastructure, tools, technologies, and other related services; advanced algorithms and data visualization applications; access to discounted software products and applications information, expertise, and training (NIH, 2021).
Center for Scientific Review (CSR)	Since 1946, the Center for Scientific Review (CSR) has worked to see that NIH grant applications receive fair, independent, expert, and timely scientific reviews—free from inappropriate influences—so NIH can fund the most promising research (CSR, 2021).
Fogarty International Center (FIC)	The Fogarty International Center (FIC) is dedicated to advancing the mission of the National Institutes of Health (NIH) by supporting and facilitating global health research conducted by U.S. and international investigators, building partnerships between health research institutions in the U.S. and abroad, and training the next generation of scientists to address global health needs (Fogarty International Center, 2021).
National Center for Advancing Translational Sciences (NCATS)	The mission of the National Center for Advancing Translational Sciences (NCATS) is to catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions (NCATS, 2021).
National Center for Complementary and Integrative Health (NCCIH)	The mission of the National Center for Complementary and Integrative Health (NCCIH) is to determine, through rigorous scientific investigation, the fundamental science, usefulness, and safety of complementary and integrative health approaches and their roles in improving health and health care (NCCIH, 2021).

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## **Appendix F**

### **NIH Office of Autoimmune Disease Research Act of 1999**



106TH CONGRESS  
1ST SESSION

# S. 1897

To amend the Public Health Service Act to establish an Office of Autoimmune Diseases at the National Institutes of Health, and for other purposes.

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IN THE SENATE OF THE UNITED STATES

NOVEMBER 9, 1999

Mr. BIDEN introduced the following bill; which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

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## A BILL

To amend the Public Health Service Act to establish an Office of Autoimmune Diseases at the National Institutes of Health, and for other purposes.

1       *Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,*  
2       **3 SECTION 1. SHORT TITLE.**

4       This Act may be cited as the “NIH Office of Auto-  
5       immune Diseases Act of 1999”.

6       **6 SEC. 2. ESTABLISHMENT OF OFFICE OF AUTOIMMUNE DIS-  
7                  EASES AT NATIONAL INSTITUTES OF HEALTH.**

8       Title IV of the Public Health Service Act (42 U.S.C.  
9       281 et seq.) is amended by inserting after section 404D  
10      the following section:

## 1                   “AUTOIMMUNE DISEASES

2         “SEC. 404E. (a) ESTABLISHMENT.—There is estab-  
3         lished within the Office of the Director of NIH an office  
4         to be known as the Office of Autoimmune Diseases (in  
5         this section referred to as the ‘Office’), which shall be  
6         headed by a Director appointed by the Director of NIH.

## 7         “(b) DUTIES.—

8                   “(1) IN GENERAL.—The Director of the Office,  
9         in consultation with the coordinating committee es-  
10        tablished under subsection (e), shall carry out the  
11        following:

12                  “(A) The Director shall recommend an  
13         agenda for conducting and supporting research  
14         on autoimmune diseases through the national  
15         research institutes. The agenda shall provide  
16         for a broad range of research and education ac-  
17         tivities relating to biomedical, psychosocial, and  
18         rehabilitative issues, including studies of the  
19         disproportionate impact of such diseases on  
20         women.

21                  “(B) The Director shall with respect to  
22         autoimmune diseases promote coordination and  
23         cooperation among the national research insti-  
24         tutes and entities whose research is supported  
25         by such institutes.

1                 “(C) The Director shall promote the ap-  
2                 propriate allocation of the resources of the Na-  
3                 tional Institutes of Health for conducting and  
4                 supporting research on autoimmune diseases.

5                 “(D) The Director shall annually prepare a  
6                 report that describes the research and edu-  
7                 cation activities on autoimmune diseases being  
8                 conducted or supported through the national re-  
9                 search institutes, and that identifies particular  
10                 projects or types of projects that should in the  
11                 future be conducted or supported by the na-  
12                 tional research institutes or other entities in the  
13                 field of research on autoimmune diseases.

14                 “(2) PRINCIPAL ADVISOR REGARDING AUTO-  
15                 IMMUNE DISEASES.—With respect to autoimmune  
16                 diseases, the Director of the Office shall serve as the  
17                 principal advisor to the Secretary, the Assistant Sec-  
18                 retary for Health, and the Director of NIH, and  
19                 shall provide advice to the Director of the Centers  
20                 for Disease Control and Prevention, the Commis-  
21                 sioner of Food and Drugs, and other relevant agen-  
22                 cies.

23                 “(c) COORDINATING COMMITTEE.—The Director of  
24                 NIH shall ensure that there is in operation a committee  
25                 to assist the Director of the Office in carrying out sub-

1 section (b), that the committee is designated as the Auto-  
2 immune Diseases Coordinating Committee, and that, to  
3 the extent possible, such Coordinating Committee includes  
4 liaison members from other Federal health agencies, in-  
5 cluding the Centers for Disease Control and Prevention  
6 and the Food and Drug Administration.

7       “(d) REPORT.—Not later than October 1, 2001, the  
8 Comptroller General shall prepare and submit to the ap-  
9 propriate committees of Congress a report concerning the  
10 effectiveness of the Office in promoting advancements in  
11 research, diagnosis, treatment, and prevention related to  
12 autoimmune diseases.

13       “(e) DEFINITION.—For purposes of this section, the  
14 term ‘autoimmune diseases’ includes diseases or disorders  
15 in which autoimmunity is thought to play a significant  
16 pathogenetic role, as determined by the Secretary.

17       “(f) AUTHORIZATION OF APPROPRIATIONS.—For the  
18 purpose of carrying out this section, there are authorized  
19 to be appropriated \$950,000 for fiscal year 2000, and  
20 such sums as may be necessary for each of fiscal years  
21 2001 and 2002.”.





## **Appendix G**

# **Analysis of the NIH Autoimmune Disease Research Grant Portfolio: Methodology**

### **BACKGROUND**

Congress tasked the Committee for the Assessment of NIH Research on Autoimmune Disease to assess NIH research activities on autoimmune disease. The committee responded to this task, in part, by describing NIH investments or spending on autoimmune disease research grant activities. The committee used publically available NIH data sources, primarily the Research, Condition, and Disease Categorization (RCDC) system and the RePORTER database, to conduct its analysis. They are described below, along with the methods used to describe different aspects of the research portfolio (spending on autoimmune disease research by NIH and Institute and Centers (ICs); spending on autoimmune disease research by research activity; spending on autoimmune disease research by disease; IC collaborations; clinical trials, publications, and patents associated with autoimmune disease research grants; and an analysis of study sections reviewing autoimmune disease grants).

### **RESEARCH, CONDITION, AND DISEASE CATEGORIZATION SYSTEM**

The NIH Reform Act of 2006 required NIH to prioritize consistency and transparency by creating a tool to categorize the agency's funded research. Implemented in 2008, the RCDC system "uses sophisticated text data mining (categorizing and clustering using words and multiword

phrases) in conjunction with NIH-wide definitions used to match projects to categories.<sup>1</sup> RCDC compiles a list of all the funded grants and contracts that fit into the specific categories and includes details such as funding amounts and other grant characteristics.<sup>2</sup> These categories are referred to as “spending categories.”

The RCDC categorization process enables NIH to apply the latest technology to consistently report on how America’s tax dollars are spent to support medical research.<sup>3</sup> A new spending category may be added to the system based on scientific need and/or at the request of an external source such as patients, advocacy groups, or Congress. Spending categories can also be added at the request of the Director of NIH or an IC. As of June 2021, there are 299 research/disease areas in RCDC, including the Autoimmune Disease spending category of interest to the committee. Since RCDC was implemented in 2008, research has only been categorized since then. At the time of the committee’s work, the most recent data available were for fiscal year (FY) 2020. Thus, the timeframe for the Committee’s analysis is from FY 2008 to FY 2020.

## RePORTER

RePORTER is a publically available electronic database that “allows users to search a repository of both intramural and extramural NIH-funded research projects from the past 25 years and access publications since 1980, and patents resulting from NIH funding.”<sup>4</sup> RePORTER draws from a number of internal and external databases to compile information associated with research projects. These include the electronic research administration (eRA) databases, Medline, PubMed Central, the NIH Intramural Database, and Interagency Edison (iEdison) database that contains grantee reporting on inventions and patents.<sup>5</sup> RePORTER is a dynamic database that is updated weekly. Updates include the addition of new projects as well as revisions to prior awards, which may prevent an exact replication of the data used in this report.

RCDC and RePORTER have unique purposes thus they do not share all of the same information or variables. Further, similar information or variables in RCDC and RePORTER may differ as they are published on

<sup>1</sup> <https://report.nih.gov/funding/categorical-spending#/>, <https://report.nih.gov/funding/categorical-spending/rcdc-process> (accessed December 29, 2021).

<sup>2</sup> <https://report.nih.gov/funding/categorical-spending/rcdc-process> (accessed December 29, 2021).

<sup>3</sup> <https://report.nih.gov/funding/categorical-spending/rcdc> (accessed January 4, 2022).

<sup>4</sup> <https://report.nih.gov/faqs> (accessed December 29, 2021).

<sup>5</sup> <https://report.nih.gov/faqs> (accessed December 29, 2021).

different timelines and have varying budget nuances, thus these data systems should not be directly compared. Acknowledging these nuances, the committee drew upon information from both data sources in order to adequately analyze autoimmune disease research funding.

### Autoimmune Disease Spending Methodology

The committee used the NIH RePORTER database to evaluate funding and other aspects of the NIH autoimmune disease research portfolio. The RePORTER database allows users to query or search by the spending categories specified by RCDC (presented as “NIH Spending Category” in the RePORTER advanced projects search). The committee focused its analysis on the autoimmune spending category.

The committee conducted the following search in RePORTER:  
Advanced Projects Search:

Fiscal Year:

- 2008, 2009, 2010, 2011, 2012, 2013
- 2014, 2015, 2016, 2017, 2018, 2019, 2020

Project Details:

- NIH Spending Category: Autoimmune Disease
- Agency /Institute/Center: NIH

Once the search results were generated, they were exported into Excel along with optional variables (project description, project details, personnel, funded organization, project funding). A maximum of 15,000 projects can be downloaded into Excel at a time, thus, four combinations of the above search criteria were exported. Two exported datasets did not include information on the ICs that funded the grants (FY 2008–2013 and FY 2014–2020); these datasets were combined and used to conduct NIH level analyses. The two datasets (2008–2013 and 2014–2020) containing information on funding ICs were also combined and used to conduct IC level analyses. When a research project application is funded by more than one IC, it is listed once for each IC. For example, if a grant application was co-funded by two ICs it will appear in the dataset twice.

The two datasets described above were used as the source for the majority of the committee’s analyses and are referred to as the Committee RePORTER Datasets (CRD).

The following figures and tables that describe spending on autoimmune disease research were prepared using the datasets.

This methodology is associated with the analyses in Figures 6-1 and 6-2 and Tables 6-1 and 6-2.

### Categorization of Grants by Autoimmune Diseases of Interest

For a number of analyses the committee was interested in reporting data by the autoimmune diseases they chose to focus on. To carry out those analyses, CRD data were summarized or rolled up into “grants.” An explanation of the method used to do this follows.

Exported RePORTER datasets contain a row of information for each funded grant application, including the total dollar amount awarded for each year. For example, a 5-year grant awarded between 2008 and 2020 will appear as five separate rows with the same grant number, though there may be variation among project descriptions, details, and funding in the dataset. When the CRD data set was exported, there were 28,148 rows of funded grant applications. To review the data at the grant level (as opposed to the yearly grant application level), grant applications were aggregated by the project or grant number; this resulted in a total of 8,470 grants. Grants were then categorized by disease, using RCDC spending categories (based on the committee’s disease selection, RCDC categories are available for inflammatory bowel disease, multiple sclerosis, psoriasis, rheumatoid arthritis, and systemic lupus erythematosus), and using MeSH terms<sup>6</sup> and natural language processing software for diseases without a RCDC category (antiphospholipid syndrome, autoimmune thyroid disease, celiac disease, primary biliary cholangitis, Sjögren’s, type 1 diabetes). Hashimoto’s disease and Graves’ disease were combined into a single “autoimmune thyroid disease” category. Grants can be counted in more than one disease category. Grants that were not associated with any specific disease categories were labeled as “other autoimmune disease.” This methodology applies to all tables and figures that provide analyses by the committee’s autoimmune diseases of interest.

### Creation of New Dataset Variables

Two new variables were created to support specific committee analyses related to the type of research funded, and to provide a more complete estimate of the total cost of autoimmune disease research funding. These new variables are described below.

#### *Autoimmune Disease Spending by Research Type*

The committee sought to analyze NIH’s autoimmune disease research portfolio by type of research (investigator-initiated, solicited,

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<sup>6</sup> MeSH terms are produced by the National Library of Medicine and are used for indexing, cataloging, and searching of biomedical and health-related information <https://www.ncbi.nlm.nih.gov/mesh/>, accessed December 31, 2021).

and intramural research) and funding. This analysis provides insights into how NIH allocates its funds across these research activities and trends over time. To identify research type, Funding Opportunity Announcement (FOA)<sup>7</sup> numbers were examined. Within each CRD, a new variable “Type of Research” was created.

- If the FOA number was a Request for Application (RFA) or Request for Proposal (RFP), it was categorized as solicited research.
- If the FOA number was a Program Announcement (PA), it was categorized as investigator-initiated research.
- If the Activity Code<sup>8</sup> started with Z, it was categorized as intramural research.
- If the FOA number was blank, it was categorized as Unknown.

If the type of research is Unknown, it was not included in the Type of Research analysis. The FOA field may be blank in some cases such as non-grant records (contracts and intramural records), and older grant records from a time when it was not required to submit a grant in response to a FOA. Because intramural research does not have an FOA, the designated intramural activity code (Z) was used to determine the type of research.

The new variable, Type of Research, is used in the analyses associated with Figure 6-9 and Table 6-7.

#### *Combined Total Cost of Funded Autoimmune Research*

The committee noted differences in funding information available in RCDC and RePORTER early in its analysis of spending on autoimmune disease research. Due to the different purposes of the data systems, neither system provides a complete estimate of the total cost of autoimmune disease research funding by IC. The committee created a new variable, Combined Total Cost of Funded Autoimmune Research to address this issue and added it to the CRD.

There are two types of projects found in the CRD, projects that stand alone and subprojects. A subproject is a “discrete and clearly identifiable

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<sup>7</sup> An FOA number for solicited research contains the type of FOA, NIH funding Institute code, fiscal year, and associated serial number (e.g., RFA-TR-21-101). An FOA number for investigator-initiated research contains the type of FOA, fiscal year, and associated serial number (e.g., PAR-21-045). <https://grants.nih.gov/grants/guide/description.htm>, [https://grants.nih.gov/grants/guide/parent\\_announcements.htm](https://grants.nih.gov/grants/guide/parent_announcements.htm); <https://grants.nih.gov/funding/searchguide/index.html#>.

<sup>8</sup> An Activity Code is a 3-character code used to identify a specific category of extramural activity to differentiate the wide variety of research-related programs NIH supports. <https://grants.nih.gov/grants/glossary.htm>.

segment of a multicomponent application...most commonly subprojects are part of the M, P, S, and U mechanisms.<sup>9</sup> Stand-alone projects have a designated funding IC(s) in the RePORTER database, but subprojects do not; subproject funding by IC is only available as part of RCDC reporting. The committee needed this information in order to determine how much funding each IC contributed to autoimmune disease research. Out of necessity, the committee used RCDC data to identify subproject funding by IC. RCDC datasets for each FY 2008 to 2020 were downloaded and used to inform subproject funding IC and to configure total dollar amounts in the CRD. Generally, RCDC and RePORTER should not be directly compared as they serve different purposes, are published on different timelines, and have varying budget nuances. However, funding IC dollar amounts would be significantly underestimated without utilizing both data sources. RCDC dollar amounts are frozen and may not always match the frequently updated data in RePORTER. Additionally, RePORTER separates Total Cost for projects and Total Cost for subprojects, making it challenging to determine the total amount of dollars any one IC spent on autoimmune disease research. A new variable, “Combined Total Cost of Autoimmune Disease Research,” was created to reflect consolidated funding for stand-alone projects and subprojects in one variable; it was added to the CRD.

The new variable, Combined Total Cost of Funded Autoimmune Disease Research, is used in the analyses associated with Figure 6-1 and Tables 6-1, 6-2, and 6-4.

#### *General Data Limitations*

NIH does not expressly budget by RCDC spending category. The annual spending estimates reflect amounts that change as a result of science, actual research projects funded, and the NIH budget. Further, the spending categories are not mutually exclusive. Research projects can

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<sup>9</sup> The M activity code, also known as general clinical research centers program, is an award made to an institution solely for the support of a General Clinical Research Center where scientists conduct studies on a wide range of human diseases using the full spectrum of the biomedical sciences. The P activity code, also known as program/project center grants, are large, multidisciplinary and long-term research efforts that generally include a diverse array of research activities. The S activity code, also known as research related programs and/or projects, includes grants for a wide range of activities including minority biomedical research support and biomedical research support shared instrumentation grants. The U activity code, also known as cooperative agreements, are a support mechanism frequently used for complex, high-priority research areas that require substantial involvement from NIH program or scientific staff (called cooperative agreements). [https://grants.nih.gov/grants/funding/ac\\_search\\_results.htm](https://grants.nih.gov/grants/funding/ac_search_results.htm), <https://grants.nih.gov/grants/glossary.htm>.

be included in multiple spending categories so amounts may add up to more than 100 percent of NIH-funded research. Additionally, the specific amounts associated with multiple spending categories are not specified. For example, hypothetical Grant A with a total cost of \$100,000 has three associated spending categories: autoimmune disease, cancer, cardiovascular. Although the data do not provide information on the percentage of dollars allocated to each of the spending categories (because the categories are defined irrespective of the budget), the total amount is considered to be dollars that supported autoimmune disease research (the autoimmune disease spending category).

Another limitation is that NIH actual total obligations reported by the Office of the Budget are not provided for autoimmune disease research. Because these dollar amounts come from exclusive sources, the committee was unable to directly compare them. Despite the nuances in data sources, the committee was able to gauge the percentage of autoimmune disease spending across NIH compared to NIH actual total obligations as seen in the analysis associated with Figure 6-1 and Table 6-1.

### **Methods for Additional Specific Analyses**

#### *IC Collaboration*

An Excel pivot table was created within the CRD containing funding ICs from FY 2008-2020 to examine the relationship between the IC administering a grant and ICs that contribute funding to the grant. An administrative IC with at least one funding IC was considered a collaboration, also known as joint IC funding. To determine the average number of joint IC funding collaborations over the period, the number of collaborations were summed and divided by 13 (years). The range of joint IC funding collaborations per year included the least amount of collaborations in a given year within the committee's specified time period, and the most amount of collaborations in a given year within the time period, by IC. This methodology was used in the analyses associated with Table 6-8.

#### *Study Section Analysis*

The committee used the online CSR study section tool available at <https://public.csr.nih.gov/StudySections>.<sup>10</sup> The committee entered the name of each of the select autoimmune diseases of committee interest into the study section search field to identify the names of its associated chartered study sections. Only chartered study sections were included

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<sup>10</sup> Accessed November 24, 2021.

because they review most investigator-initiated research grant applications. The total number of chartered study sections for all select diseases (de-duplicated) was then tallied.

The committee used the RePORTER Matchmaker search tool available at <https://reporter.nih.gov/matchmaker>.<sup>11</sup> The committee entered the name of each of the select autoimmune diseases of committee interest into the field to yield the number of projects associated with that disease. The user then activated the Active Projects feature and selected 2019 and 2020 in the Fiscal Year dropdown. RePORTER then generated a graph of the study sections that had reviewed the most grants for that autoimmune disease. The study sections appearing in the graph, and the number of grants each study section reviewed, constitute the data included in Table 6-10.

### *Clinical trials*

Using clinicaltrials.gov, 637 clinical trials were identified and exported. Clinical trials were then linked to the 8,470 autoimmune disease grants of interest using a matching algorithm. The National Academies staff then manually reviewed the clinical trials to ensure that they were related to the committee's autoimmune diseases of interest or the other autoimmune disease category. This resulted in a total of 353 clinical trials used in the analysis. This methodology was used in the analyses associated with Figure 6-26.

### *Publications*

To determine the publications associated with the autoimmune disease grants of interest, a variety of NIH and public databases were used, including PubMed, Scientific Publication Information Retrieval and Evaluation System (SPIRES) bibliometric tools, and Web of Science (WoS). SPIRES linked peer-reviewed publications to the autoimmune disease grants of interest. Disease information for publications is based on the disease categorization of associated grants. To characterize scientific productivity and impact, the list of related publications associated with the grants of interest were analyzed using the following metrics: total number of publications, number of publications by disease type, and publication distribution over time from publication year 2008 to 2020. Relative Citation Ratios (RCRs) were retrieved from iCite, a tool created by the Office of Portfolio Analysis within NIH, to access bibliometrics for relevant publications. Journal impact factor was obtained from WoS for the articles

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<sup>11</sup> Accessed December 3, 2021.

publication year. This methodology was used in the analyses associated with Figures 6-27, 6-28, and 6-29, and Table 6-12.

### *Patents*

Patent data (patent and patent applications) were gathered from the U.S. Patent Databases (USPTO) and RePORTER. Patent data was linked to 8,470 autoimmune disease grants of interest using a matching. All linked data are in the public domain. Disease information for patent applications and patents is based on the disease categorization of associated grants. This methodology was used in the analyses associated with Figures 6-30 and 6-31.



# **Appendix H**

## **Topic Analysis of NIH Autoimmune Disease Research Grant Abstracts**

*Authored by:<sup>1</sup> Chris Barousse<sup>2,3</sup>*

### **INTRODUCTION**

In 2019, Congress tasked the National Academy of Sciences, Engineering and Medicine (the National Academies) to evaluate National Institutes of Health (NIH) research on autoimmune disease. The scope of work for the committee included a review of trends in the focus (topics) of autoimmune disease research. The goal of this paper is to provide insight into the most popular research topics associated with 8,470 NIH autoimmune disease research grant abstracts using latent dirichlet allocation (LDA), a statistical modeling technique used in natural language processing.

### **BACKGROUND**

LDA is a popular, well-documented statistical method used in natural language processing (NLP) settings. LDA groups what the NLP field refers to as a corpus of texts by “latent” topics, which are found by looking at the similarity of the texts’ contents (Blei et al., 2003). As of 2021, the original paper describing LDA methodology has been cited 5,714 times. Several software packages in the R statistical language can implement LDA, and this method has been applied specifically to scientific abstracts to analyze funding patterns and trends in research (Bittermann and Fischer, 2018; Park et al., 2016; Porturas and Taylor, 2021).

An LDA model consists of probabilities for each word belonging to each topic, and probabilities of each document belonging to each topic. LDA makes several assumptions about the corpus. First, it assumes that

each document is a collection of words and disregards the sequence and grammar of the document; this is called the bag-of-words model. Second, LDA assumes that the corpus contains knowledge about many topics  $k$  and that the user has already removed words that are either too rare or too common and stopwords, which are words that do not provide any meaningful information and in most situations include pronouns, prepositions, articles, and conjunctions. If words are sparse throughout the corpus, the model will take a long time to search through the corpus finding the rare words. Including words that are too common will generate topics that are too similar to each other and make discerning between them difficult. LDA sees documents as consisting of one or more words, and words can belong to one or more topics with a different probability of belonging to each topic.

The LDA algorithm is iterative, meaning that the user must decide how many times it is run on a corpus. Running it more increases the chance of finding distinct topics, but running LDA is time and computationally intensive. First, each word is randomly assigned a probability for belonging in topic  $t$ . The code then goes through each word  $w$  belonging to document  $d$  and computes the proportion of words in the document  $d$  that are assigned to the topic  $t$ , the proportion of assignments to topic  $t$  over all the documents that contain the word  $w$ , and the updated probability of the word  $w$  belonging to topic  $t$ . Averaging the probabilities of each word belonging to a specific topic gives the topic probabilities for each document.

## Methods

LDA works well to “assess trends in the focus of NIH research and address whether the trends are reflective of the changes in epidemiology as compared to other factors such as availability of research tools and technologies, and emerging biomedical knowledge and concepts” (NASEM, 2021). Given a set of 8,470 NIH research grant abstracts related to autoimmune diseases that were funded between 2008 and 2020, topic modeling using LDA was implemented to discern which topics are prevalent within the abstracts.

In preparing the grant abstracts for analysis, words that were too common in the abstracts, including the words research and studies, were removed. Because there was no pre-determined value of  $k$  to use, coherence scores were calculated to determine an optimal number of topics (Syed and Spruit, 2017). Coherence is a measure of how similar words within a topic are and how distinct topics are from each other. Coherence is calculated on a full LDA model; this means that the LDA algorithm was run 60 times to compare 60 values of  $k$ . Figure H-1 is a plot that calculates

the coherence of models fit using various values of  $k$ , the number of topics. A higher coherence score implies that the topics generated using  $k$  number of topics fit the data well. In consultation with the committee, it was decided to use the model specified with 30 topics.

Once the LDA model was chosen, the names of the 30 topics needed to be determined. LDA does not assign a name to the topics, and it is common practice to look at the top words assigned to each topic to determine what ideas each topic is trying to convey. There is no significance in the numbers associated with each topic or the order of topics given by the model. Figure H-2 shows the top 10 most frequent words assigned to each topic. In consultation with committee members, a name was assigned to each topic. Table H-1 lists the final topic names; some topics were given the same topic name because they were deemed too similar, and their topic assignments were combined in the later plots.

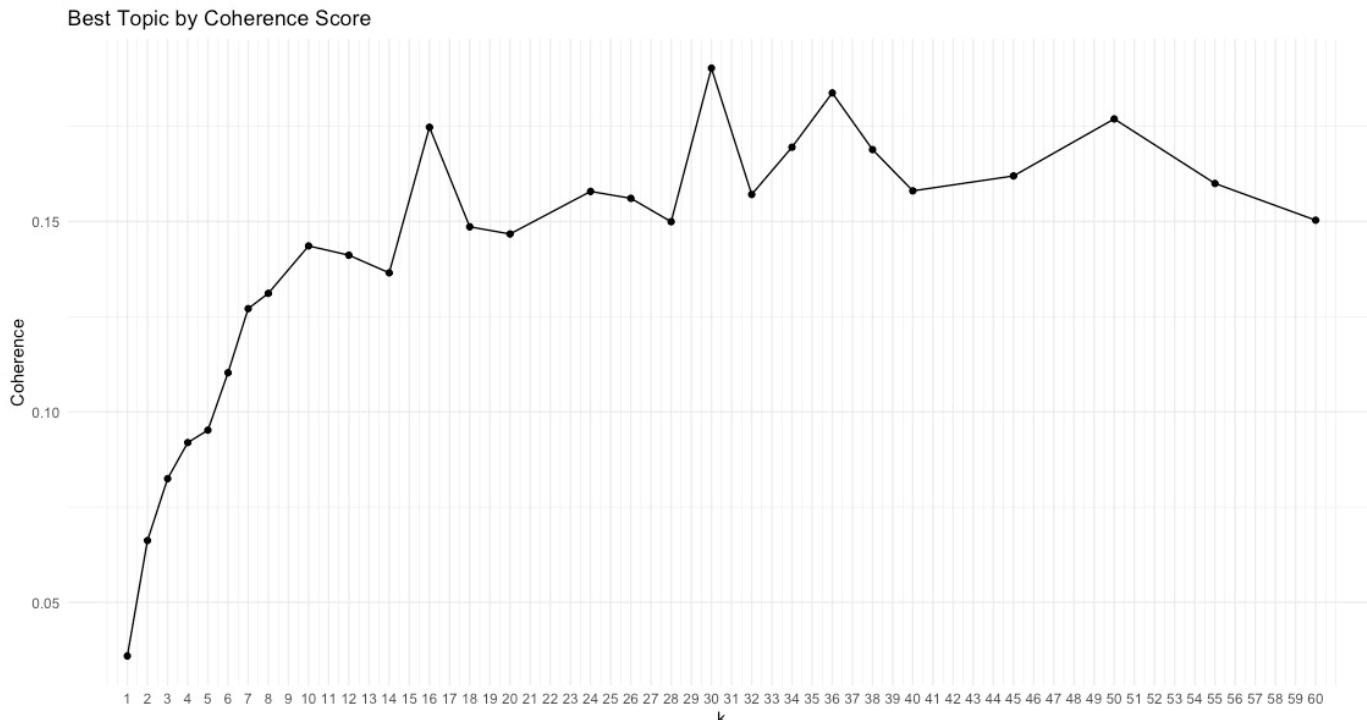
## Final Results

One of the outputs of the LDA model is the theta matrix, which shows the proportion of topics assigned to each abstract. For example, 30 percent of an abstract may be attributed to topic 1, and 70 percent of it may be attributed to topic 2. Theta has  $N$  (the number of abstracts) rows and  $K$  (the number of topics) columns, and each row in the matrix sums to 1. For each fiscal year, the proportion of each topic attributed to all abstracts funded that year was summed and a separate plot was made for each topic. In other words, the y-axis is the proportion of abstracts funded in a given year that was attributed to that topic. Figure H-3 groups the topics by theme: immune response related, clinical, disease focused, and administrative.

## Conclusion

Figure H-3 can be used to determine trends in topics over time using the LDA model. Treatment/therapy, lung disease, diagnostic [tools], imaging, and inflammatory bowel disease have trended upward from 2008 in contrast to animal models, genetics, and pathogenesis, and diabetes is consistently prevalent among topics over time. Cancer, multiple sclerosis, cardiovascular, psoriasis, lung disease, and rheumatoid arthritis are also consistent over time but not as popular as diabetes. It is difficult to explain the spikes in popularity in administrative topics. This could be related to NIH funding policies or other funding pattern changes.

One of the downsides of using LDA for topic modeling is that the topics must be discovered “latent” within the texts; the topics cannot be inputted into the model algorithm. Furthermore, it would have been



**FIGURE H-1** Coherence scores for k number of topics.



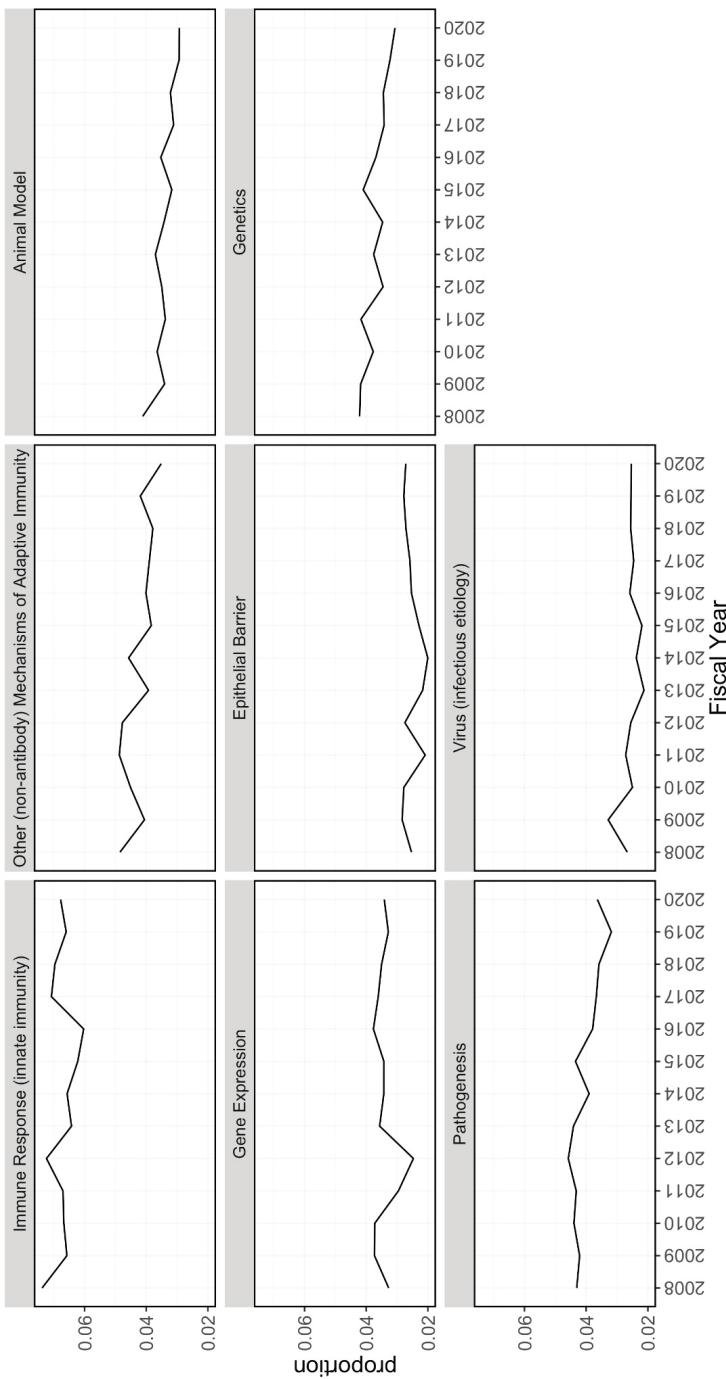
**FIGURE H-2** Top 10 words per topic.  
SOURCE: NIH, 2021.

**TABLE H-1** LDA Generated Topics for NIH Autoimmune Disease Grants, Fiscal Years 2008–2020

Topic Number	Topic Name
1	Immune Response (innate immunity)
2	Immune Response (adaptive immunity [antibodies])
3	Psoriasis
4	Other (non-antibody) Mechanisms of Adaptive Immunity
5	Centers/Core Project Funding
6	Treatment/Therapy
7	Lung Disease
8	Animal Model
9	Adaptive Immunity
10	Inflammatory Response (innate)
11	Type 1 Diabetes
12	Gene Expression
13	Epithelial Barrier
14	Type 1 Diabetes
15	Disease Progression
16	SLE
17	Cancer
18	Rheumatoid Arthritis
19	Cardiovascular
20	Centers/Core Project Funding
21	Adaptive Immunity
22	Training (funding)
23	Genetics
24	Quality of Life
25	Inflammatory Bowel Disease
26	Multiple Sclerosis
27	Pathogenesis
28	Diagnostic
29	Virus (infectious etiology)
30	Imaging

SOURCE: NIH, 2021.

### LDA Generated Topics for Autoimmune NIH Grants 2008–2020: Immune Response Related Topics

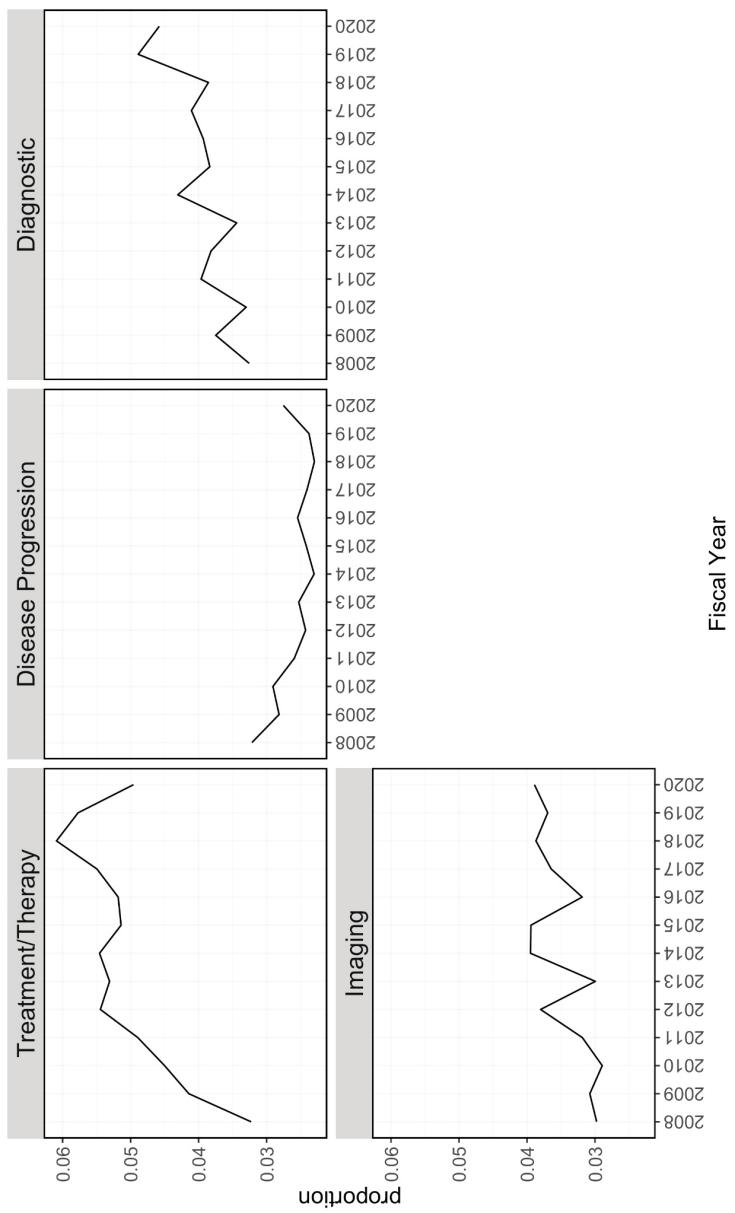


**FIGURE H-3** LDA-generated topics for NIH autoimmune disease grants, FY 2008–2020: Immune response related topics.

NOTES: FY, fiscal year; LDA, latent dirichlet allocation.

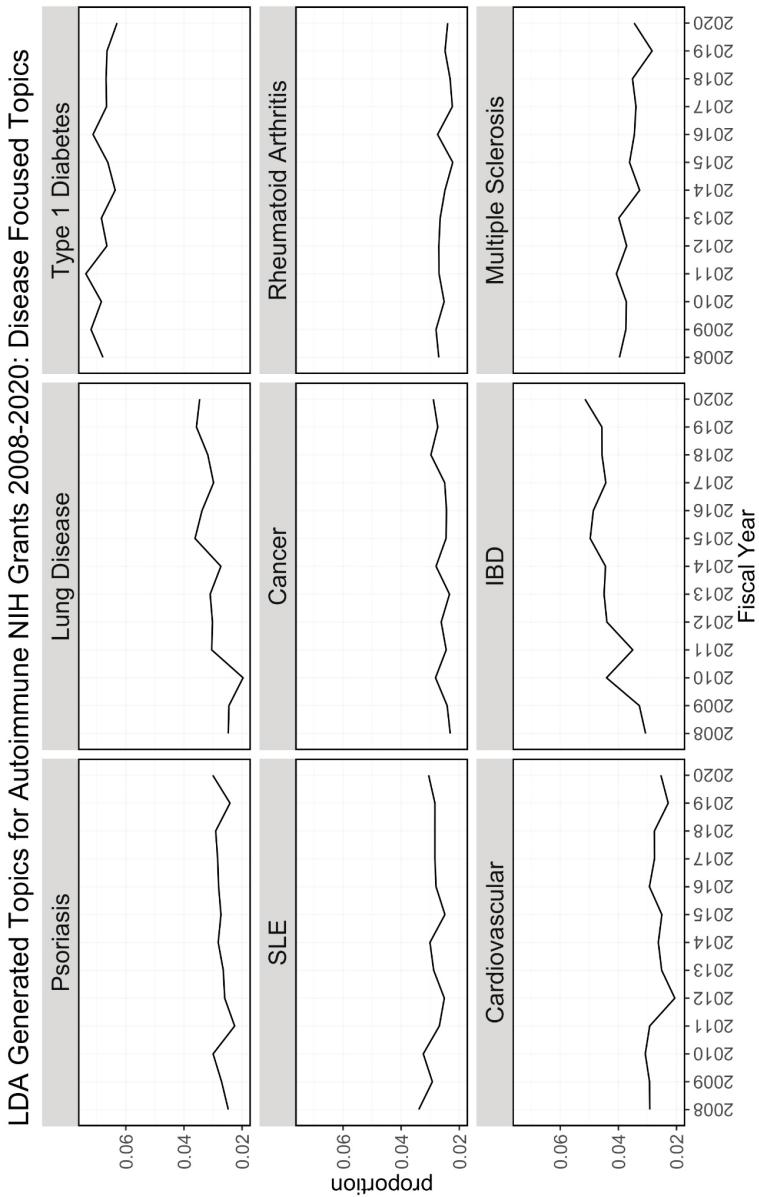
SOURCE: NIH, 2021.

LDA Generated Topics for Autoimmune NIH Grants 2008-2020: Clinical Topics

**FIGURE H-4** LDA-generated topics for NIH autoimmune disease grants, FY 2008–2020: Clinical topics.

NOTES: FY, fiscal year; LDA, latent dirichlet allocation.

SOURCE: NIH, 2021.



**FIGURE H-5** LDA-generated topics for NIH autoimmune disease grants, FY 2008–2020: Disease focused topics.

NOTES: FY, fiscal year; LDA, latent dirichlet allocation.

SOURCE: NIH, 2021.

LDA Generated Topics for Autoimmune NIH Grants 2008-2020: Administrative Topics

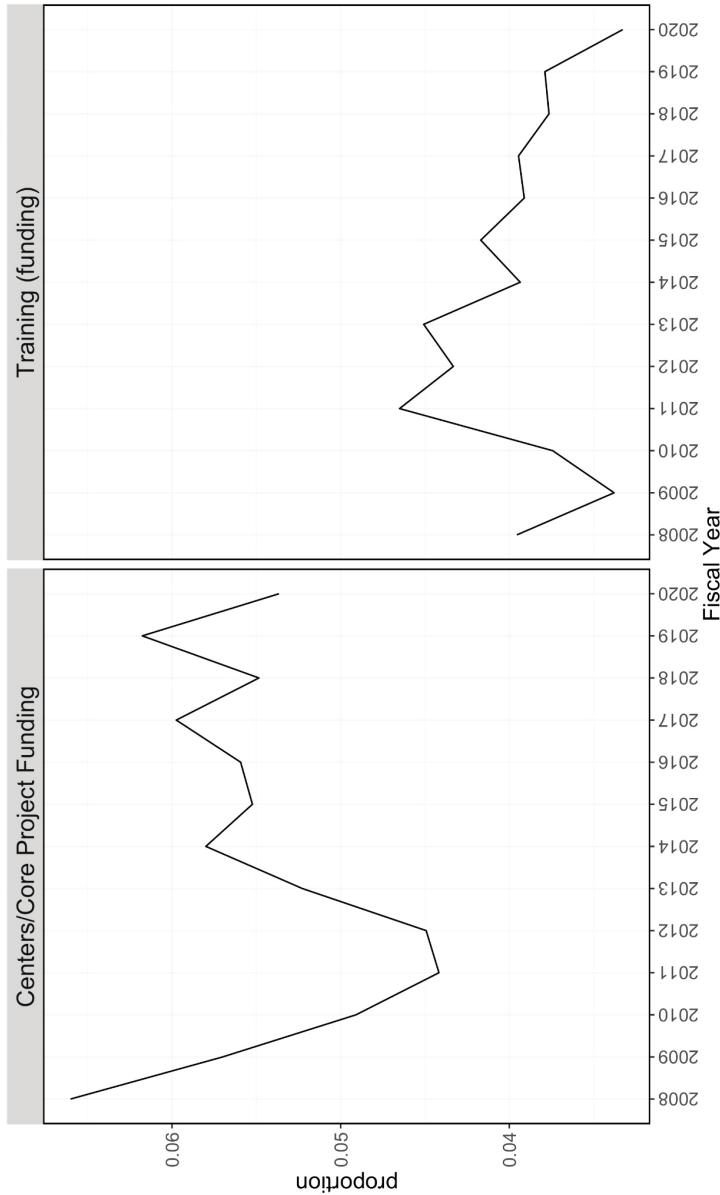


FIGURE H-6 LDA-generated topics for NIH autoimmune disease grants, FY 2008–2020: Administrative topics.

NOTES: FY, fiscal year; LDA, latent dirichlet allocation.

SOURCE: NIH, 2021.

interesting to see how popular specific diseases of interest, including celiac disease, autoimmune thyroid disease (consisting of Hashimoto and Graves' disease), antiphospholipid syndrome, primary biliary cholangitis, and Sjögren's disease, are over time. If the LDA model had been allowed to include a greater number of topics as input, the likelihood of seeing smaller, more specific topics would increase. However, increasing the number of topics could also allow the algorithm to detect groupings of words that are not meaningful as it tries to find more topics within the texts. It can be concluded from the omission of specific diseases from the final list of topics that they are not well represented within the abstracts analyzed.

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