Chapter 5: Precision Medicine and Clinical Care

The Editors

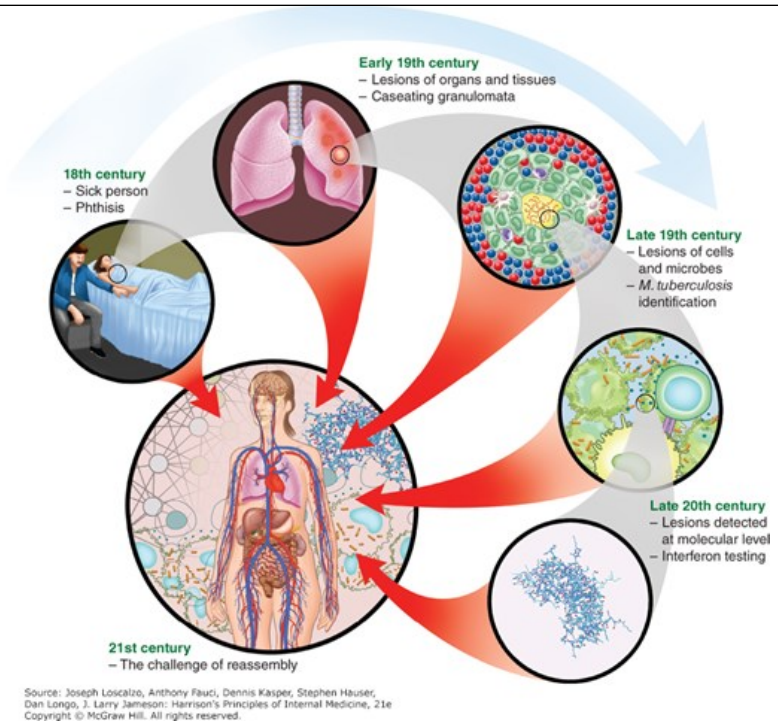
DISEASE NOSOLOGY AND PRECISION MEDICINE

Modern disease nosology arose in the late nineteenth century and represented a clear departure from the holistic, limited descriptions of disease dating to Galen. In this rubric, the definition of any disease is largely based on clinicopathologic observation. As the correlation between clinical signs and symptoms with pathoanatomy required autopsy material, diseases tended to be characterized by the end organ in which the primary syndrome was manifest and by late-stage presentations. Morgagni institutionalized this framework with the publication of *De Sedibus et Causis Morborum per Anatomen Indagatis* in 1761, in which he correlated the clinical features of patients with more than 600 autopsies at the University of Padua, demonstrating an anatomic basis for disease pathophysiology. Clinicopathologic observation served as the basis for inductive generalization coupled with the application of Occam's razor in which disease complexity was reduced to its simplest possible form. While this approach to defining human disease has held sway for over a century and facilitated the conquest of many diseases previously considered incurable, overly inclusive and simplified Oslerian diagnostics suffer from significant shortcomings. These include, but are not limited to, failure to distinguish the underlying etiology of different diseases with common pathophenotypes. For example, many different diseases can cause end-stage kidney disease or heart failure. Over time, the classification of neurodegenerative disorders or lymphomas, as well as many other diseases, is becoming more refined and precise as the underlying etiologies are identified. These distinctions are important for providing predictable prognostic information for individual patients with even highly prevalent diseases. Additionally, therapies may be ineffective owing to a lack of understanding of the often subtle molecular complexities of specific disease drivers.

Beginning in the mid-twentieth century, the era of molecular medicine offered the idealized possibility of identifying the underlying molecular basis of every disease. Using a conventional reductionist paradigm, physician-scientists explored disease mechanism at ever-increasing molecular depth, seeking the single (or limited number of) molecular cause(s) of many human diseases. Yet, as effective as this now conventional scientific approach was at uncovering many disease mechanisms, the clinical manifestations of very few diseases could be explained on the basis of a single molecular mechanism. Even knowledge of the globin β chain mutation that causes sickle cell disease does not predict the many different manifestations of the disease (stroke syndrome, painful crises, and hemolytic crisis, among others). Clearly, the profession had expected too much from oversimplified reductionism and failed to take into consideration the extraordinary biologic variety and its accompanying molecular and genetic complexity that underpin both normal and pathologic diversity. The promise of the Human Genome Project provided new tools and approaches and unleashed efforts to identify a monogenic, oligogenic, or polygenic cause for every disease (allowing for environmental modulation). Yet, once again, disappointment reigned as the pool of genomes expanded without the expected revelations (aside from rare variants). The arc of progressive reductionism (as illustrated for tuberculosis in **Fig. 5-1**) in refining and explaining disease reached a humbling plateau, revealing the need for new approaches to understand better the etiology, manifestations, and progression of most diseases. The stage was set for a return to holism. However, in contrast to the holism of ancient physicians, we adopted one that is integrative, taking genomic context into account in all dimensions. In the course of elaborating this complex pathobiologic landscape, disease definition must become more precise and progressively more individualized, setting the stage for what we term *precision medicine*.

FIGURE 5-1

Arc of reductionism in medicine. *(From JA Greene, J Loscalzo. Putting the patient back together—social medicine, network medicine, and the limits of reductionism. N Engl J Med 377:2493, 2017. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)*



Oversimplification of phenotype is a natural outgrowth of the observational scientific method. Categorizing individuals as falling into groups or clusters that are reasonably similar simplifies the task of the diagnostician and also facilitates the application of "specific" therapies more broadly. Biomedicine has been viewed as less quantitative and precise than other scientific disciplines, with biologic and pathobiologic diversity (biologic "noise") viewed as the norm. Thus, distilling such observational complexity to a fundamental group of symptoms or signs that are reasonably invariant across a group of sick individuals has served as the basis for the approach to disease and its treatment since the earliest days of medicine. This approach to diagnosis and therapy has remained in place into the twenty-first century, serving as the basis for the development of standard diagnostic tests and of broadly applied drug therapies. Targeting larger groups of patients is efficient when applied to large populations. As successful as this approach has been in advancing medical care, it is important to point out its limitations, which include significant predictive inaccuracies and sizeable segments of the disease population who do not respond to the most "effective" drugs (upward of 60% by some estimates). Clearly, a more nuanced approach to diagnosis and therapy is required to achieve better prognostic and therapeutic outcomes.

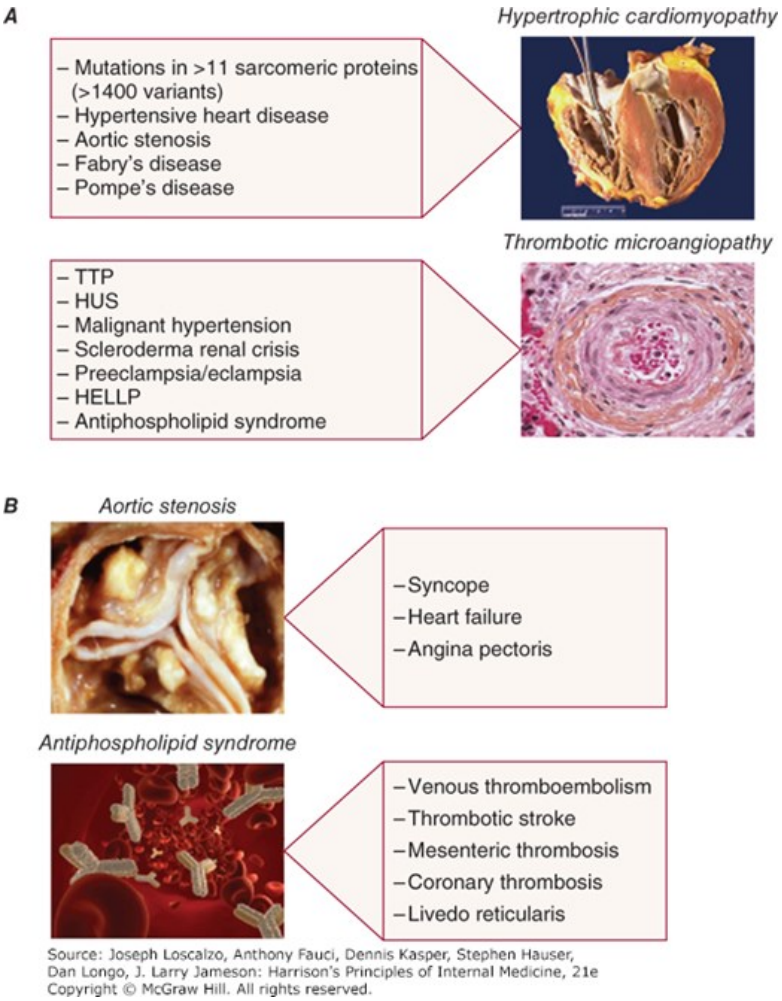
Turning first to phenotype, astute clinicians know full well the subtle and vivid differences in presentation that are often manifest among individuals with the same disease. In some cases, these differences in pathophenotype lead to new subclassifications of the disease, such as heart failure with preserved ejection fraction versus heart failure with reduced ejection fraction. Often, these relatively crude efforts at making diagnoses more precise are driven by new technologies or new ways of applying established technologies. In other cases, differences in pathophenotype are more subtle, not necessarily clinically apparent, and often driven by measures of endophenotype, such as distinctions among vasculitides facilitated by refinements in serologies or immunophenotyping. The impetus to create these subclasses of disease is largely determined by the need to improve prognosis and apply more precise and effective therapies. Based on these guiding principles, many experienced clinicians will argue—and rightly so—that they have been practicing personalized, precision medicine throughout their careers: they characterize each patient's illness in great detail, and choose therapies that respect and are guided by those individualized clinical and laboratory features, limited though they may be.

For many diseases, genomic variation, whether inherited or acquired, provides opportunities to refine diagnostic precision with even greater fidelity and predictive accuracy. For this reason, the field of precision medicine has now entered a new era that couples the molecular reductionism of the last century with an integrative, systems-level understanding of the basis for pathophenotype. Equally important, modern genomics has established that genomic context, sometimes referred to as modifier genes, is distinctive for each individual person; hence, understanding that context provides the insight necessary to predict how a primary disease driver or drivers may manifest a clinical pathophenotype—e.g., why some individuals with sickle cell anemia will develop stroke, while others will develop acute chest syndrome. *This concept that primary genetic and/or environmental drivers of a disease differentially affect disease expression based on an individual's unique genomic context serves as the ultimate basis for much of what we denote as precision medicine.*

To develop a precision medicine strategy for any disease, the clinician needs to be aware of two important, confounding principles. First, patients with different diseases can manifest similar pathophenotypes, i.e., *convergent phenotypes.* Examples of this principle include the hypertrophied myocardium found in hypertrophic cardiomyopathy, infiltrative cardiomyopathies, critical aortic stenosis, and untreated, long-standing hypertension; and the thrombotic microangiopathy found in malignant hypertension, scleroderma renal crisis, thrombotic thrombocytopenic purpura, eclampsia, and antiphospholipid syndrome. Second, patients with the same basic disease can manifest very different pathophenotypes, i.e., *divergent phenotypes* **(Chap. 466)**. Examples of this principle include the different clinical manifestations of cystic fibrosis or sickle cell disease and the incomplete penetrance of many common genetic diseases. These common presentations of different diseases and different presentations of the same disease are both a consequence of genomic context coupled with unique exposures over an individual's lifetime **(Fig. 5-2)**. Understanding the interplay among these many complex molecular determinants of disease expression is essential for the success of precision medicine.

FIGURE 5-2

Convergent and divergent phenotypes. Examples of the former (***A***) include hypertrophic cardiomyopathy and thrombotic microangiopathy, and examples of the latter, and (***B***) include aortic stenosis and antiphospholipid syndrome, each of which can have several distinct clinical presentations. HELLP, hemolysis, elevated liver enzymes, and a low platelet count; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura.



Given the complexity of the genomic and environmental context of an individual, one must ask the question: How precise do we need to be in order to practice effective precision medicine? Complete knowledge of a person's comprehensive genome (DNA, gene expression, mitochondrial function, proteome, metabolome, posttranslational modification of the proteome, and metagenome, among others) and quantitative assessments of environmental and social history are not possible to acquire; yet, this shortcoming does not render the general problem intractable. Owing to the fact that the molecular networks that govern phenotype are overdetermined (i.e., redundant) and that there are primary drivers of disease expression that are modified in a weighted way by other genomic features of an individual, the practice of precision medicine can be realized without complete

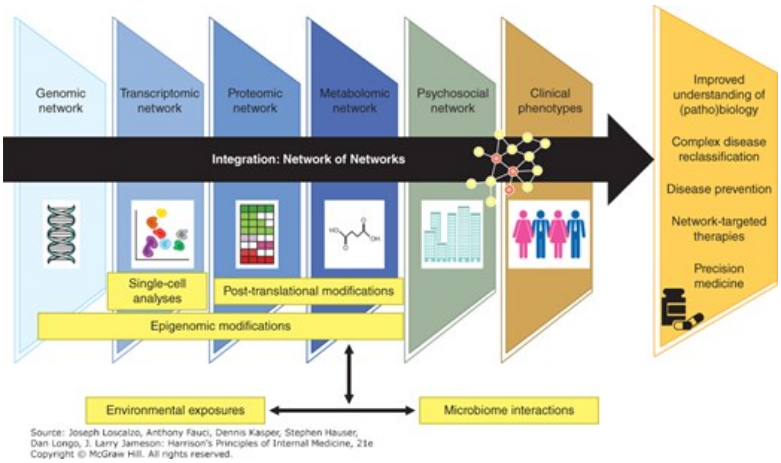
knowledge of all dimensions of the genome. Examples of how best to realize this strategy are discussed later in this chapter.

REQUIREMENTS FOR PRECISION MEDICINE

The essential elements of any precision medicine effort include phenotyping, endophenotyping (defining the characteristics of a disorder that are not readily observable), and genomic profiling **(Fig. 5-3)**. While subtle distinctions among individuals with the same disease are well known to clinicians, formalizing these nuanced differences is critical for achieving more precise phenotypes. Deep phenotyping requires a detailed history, including family history and environmental exposures, as well as relevant (physiologic) functional studies and imaging, including molecular imaging where appropriate. Biochemical, immunologic, and molecular tests of body fluids provide additional detail to the overall phenotype. Importantly, these objective laboratory tests together with functional studies compose an assessment of the endophenotype (or endotype) of an individual, refining the overall discriminant power of the evaluation. One additional concept that has gained traction in recent years is the notion of orthogonal phenotyping, i.e., assessing clinical, molecular, imaging, or functional (endo)phenotypes seemingly unrelated to the clinical presentation. These features further enhance the ability to distinguish (sub)phenotypes and derive from the fact that diseases can be subtly (subclinically) manifest in organ systems different from that in which the primary symptoms or signs are expressed. While some diseases are well known to affect multiple organ systems (e.g., systemic lupus erythematosus) and in many cases involvement of those many systems is assessed at initial diagnosis, such is not the case for most other diseases. As we begin to understand the differences in the organ-specific expression of genomic variants that drive or modify disease, it is becoming increasingly apparent that orthogonal—or more appropriately, unbiased comprehensive—phenotyping should become the norm.

FIGURE 5-3

Universe of precision medicine. The totality of precision medicine incorporates multidimensional biologic networks, the integration of which leads to a network of networks whose components interact with each other and with environmental exposures to yield a distinctive phenotype or pathophenotype. *(Reproduced with permission from LY-H Lee, J Loscalzo: Network medicine in pathobiology. Am J Pathol 189:1311, 2019.)*

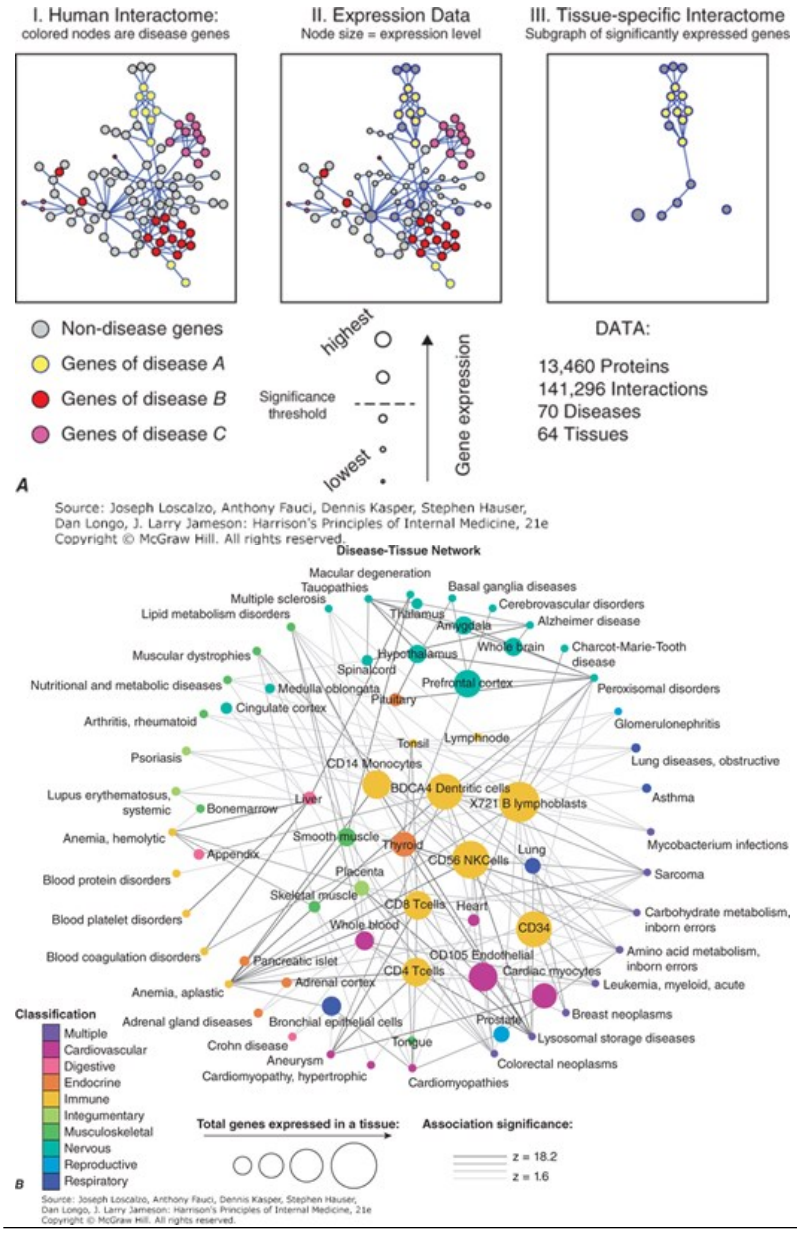


Genomic profiling must next be coupled to detailed phenotyping. The complex levels of genomic assessment continue to mature and include DNA sequencing (exomic, whole genome), gene expression (mRNA and protein expression), and metabolomics. In addition, the epigenome, the posttranslationally modified proteome, and the metagenome (the personal microbiome of an individual) are gaining traction as additional elements of comprehensive genomics **(Chap. 483)**. Not all of these genomic features are yet available for clinical laboratory testing, and those that are available are largely confined to blood testing. While DNA sequencing using whole blood would generally apply to any organ-based disease, gene expression, metabolomics, and epigenetics are often tissue specific. As tissue specimens cannot always or easily be obtained from the organ of interest, attempts at correlating whole-blood mRNA, protein, or metabolite profiles with those of the involved organ are critical for precise prognostics and therapeutic choices. In many cases, systemic consequences to an organ-specific disease (e.g., systemic inflammatory responses in individuals with atherosclerosis) can be ascertained and may provide useful prognostic information or therapeutic strategies. These biomarker signatures are the subject of ongoing discovery and have provided useful guidance toward improved diagnostic precision in many diseases. However, in many diseases, the correlations between these plasma or blood markers and organ-based diseases are weak, indicating a need to analyze each condition and each resulting signature before applying it to clinical decision-making. It is important to note that one of the key determinants of the functional consequences of a genetic variant believed to drive a disease phenotype is not simply its expression in a tissue of interest but, more importantly, the coexpression of protein

binding partners in that same tissue comprising specific (dys)functional pathways that govern phenotype **(Fig. 5-4)**. An alternative strategy currently under investigation is the conversion of induced pluripotent stem cells from a patient into a cell type of interest for gene expression or metabolomics study. As rational as this approach seems from first principles, it is important to note that gene expression patterns in these induced, differentiated cell types are not completely consonant with their native counterparts, offering often limited additional information at potentially great additional expense.

FIGURE 5-4

Gene expression and phenotype. ***A.*** The human protein-protein interactome is constructed, and a specific disease module is identified (I); gene expression within this module is ascertained (II); and the tissue specificity of gene expression is determined (III). This analysis leads to a reduction of the total number of disease module genes that govern phenotype in a specific organ, which is a reflection of the specific pathway (or pathways) that is (or are) expressed in their functional entirety in that tissue. ***B.*** A disease-tissue bipartite network is constructed wherein specific tissues are placed within the circle and linked to diseases shown on the circumference. Nodes are colored according to tissue classification, the sizes of nodes are proportional to the total number of genes expressed in them, and the widths (shades) of the lines or edges correspond to the significance of the associations with specific diseases. *(From M Kitsak et al: Tissue Specificity of Human Disease Module. Sci Rep 6: 35241, 2016, Figure 4.)*



While phenotype features of many chronic diseases are assessed over time, genomic features tend to be limited to single time point sampling. Time trajectories are extremely informative in precision genotyping and phenotyping, with gene expression patterns and phenotypes changing over time in different ways among different patients with the same overarching phenotype. Cost, feasible sampling frequency, predictive power, and therapeutic choices will all drive the optimal strategy for the acquisition of timed samples in any given patient; however, with continued cost reduction in genomics technologies, this limitation may be progressively mitigated and clinical application may become a reality.

One important class of diseases that does not have most of these limitations in genomic profiling is cancer. Cancers can be (and are) sampled (biopsied) frequently to monitor temporal changes in the somatically mutating oncogenome and its consequences for the limited number of well-defined oncogenic driver pathways **(Chap. 68)**. A unique limitation of cancer in this regard, however, is that the frequency of somatic mutations over time (and, especially, with treatment) is great and the functional consequences of many of these mutations unknown. Equally important, assessment of single-cell mRNA sequencing patterns demonstrates great variability between apparently similar cells, challenging functional interpretation. Lastly, in solid tumors, stromal cells interact in a variety of ways (e.g., metabolically) with the associated malignant cells, and their gene expression signatures are also modified by the changing somatic mutational landscape of the primary malignancy. Thus, while much more information can be obtained over time in most cancer patients, the interpretation of these rich data sets continues to remain largely semi-empirical.

The possibility of identifying specific therapeutic targets remains a major goal of precision medicine. Doing so requires more than simple DNA sequencing and must include analysis of some level of gene expression, ideally in the involved organ(s). In addition to demonstrating the expression of a variant protein in the organ, one must ideally also demonstrate its functional consequences, which requires ascertaining the expression of binding partner proteins and the functional pathways they comprise. To achieve this goal, a variety of approaches have been tried, one of the most successful of which is the construction of the protein-protein interactome (the interactome), which is a comprehensive network map of the protein-protein interactions in a cell or organ of interest **(Chap. 486)**. This template provides information on the subnetworks that govern a disease phenotype (disease modules), which can be further individualized by incorporating individual variants and differentially expressed proteins that are patient specific. This type of analysis leads to the creation of an individual "reticulome" or reticulotype, which links the genotype to the phenotype of an individual **(Fig. 5-5)**. Using this approach, one can identify potential drug targets in a rational way or can even repurpose existing drugs by demonstrating the proximity of a known drug target to a disease module of interest **(Fig. 5-6)**. For example, in multicentric Castleman's disease, a disorder of unclear etiology, recognition that the PI3K/Akt/mTOR pathway is highly activated led to trials with an existing, approved drug, sirolimus. Precision medicine offers additional opportunities for optimizing the utilization of a drug by assessing the individualized pharmacogenomics of its disposition and metabolism, as demonstrated for the adverse consequences of variants in *TPMT* on azathioprine metabolism and in *CYP2C19* on clopidogrel metabolism **(Chap. 68)**.

FIGURE 5-5

Reticulotype. Patient-specific genotype-phenotype relationships by multiomic network structures are depicted for three individuals. Each individual's unique molecular perturbations (genetic variants, differentially expressed genes) are examined within the context of the subject's unique integrative biologic network or reticulome derived from these multiomic analyses. These unique reticulotypes then serve as the basis for patient-specific, precision therapies. *(Reproduced with permission from LYH Lee, J Loscalzo: Network Medicine in Pathobiology. Am J Pathol 189:1311, 2019.)*

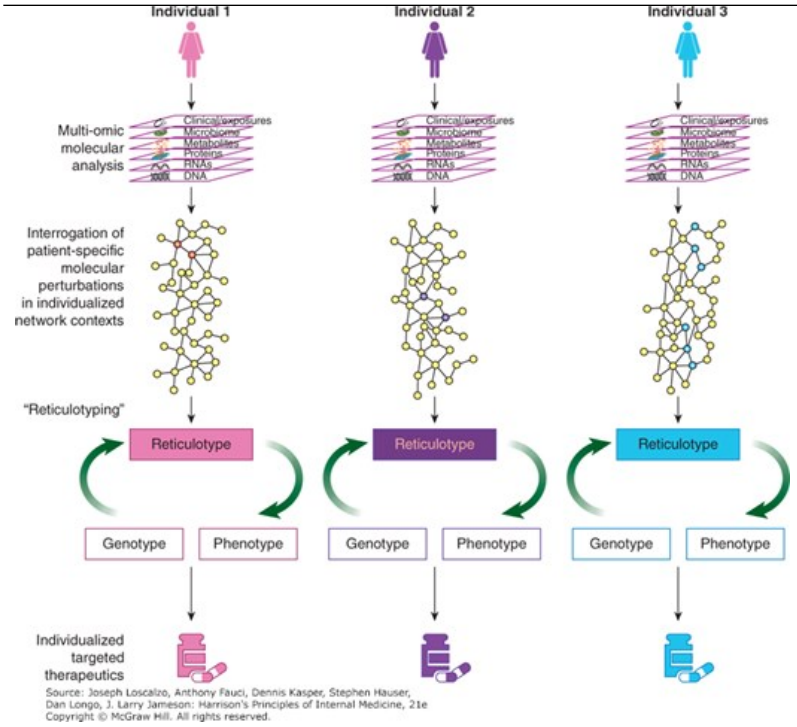
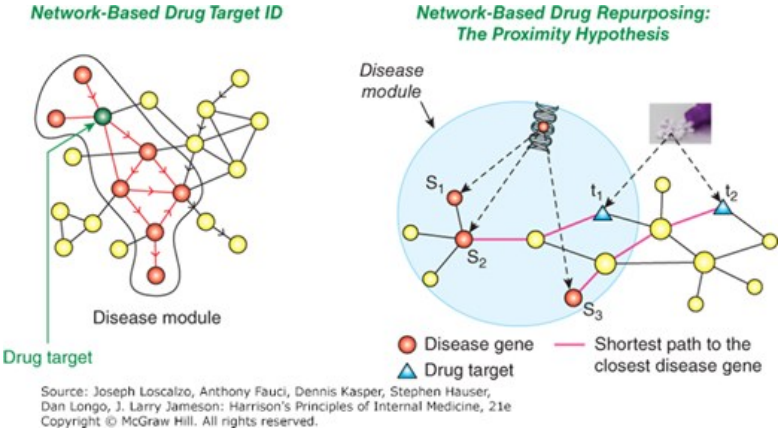


FIGURE 5-6

Network-based precision drug repurposing. *(Adapted from F Cheng et al: A genome-wide positioning systems network algorithm for in silico drug repurposing. Nat Commun 10:3476, 2019.)*



EXAMPLES OF PRECISION MEDICINE APPLICATIONS

The field of precision medicine did not appear abruptly in medical history but, rather, evolved gradually as clinicians became more aware of differences among patients with the same disease. With the advent of modern genomics, in the ideal situation, these phenotype differences can now be mapped to genotype differences. Thus, we can consider precision medicine from the perspective of the pregenomic era and the postgenomic era. Pregenomic precision medicine was applied to many diseases as therapeutic classes expanded for those disorders. A prime example of this approach is in the field of heart failure, where diuretics, digoxin, beta blockers, afterload-reducing agents, venodilators, renin-angiotensin-aldosterone inhibitors, and brain natriuretic peptide (nesiritide) are commonly used in some combination for most patients. The choice of agents is governed by the evidence basis for their use, but tailored to the primary pathophysiologic phenotypes manifest in a patient, such as congestion, hypertension, and impaired contractility. These treatments were developed in the latter half of the last century based on empiric observation, reductionist experiments of specific pathways believed to be involved in the pathophysiology, and clinical response in prospective trials. As phenotyping became more refined

(e.g., echocardiographic assessments of ventricular function and tissue Doppler characterization of ventricular relaxation), the syndrome was subclassified into heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, the latter of which does not respond well to any of the classes of therapeutic agents currently available. In the postgenomic era, ever more refined and detailed methods are under investigation to characterize pathophenotypes as well as genotypes, which may then be matched to the idealized combination of therapeutic classes of agents.

Pulmonary arterial hypertension is another disease for which definitive therapies straddle the pre- and postgenomic eras of precision medicine. Prior to the 1990s, there were no effective therapies for this highly morbid and lethal condition. With the advent of molecular and biochemical characterization of vascular abnormalities in individuals with established disease, however, therapies with agents that restored normal vascular function improved morbidity and mortality. These included calcium channel blockers, prostacyclin congeners, and endothelin receptor antagonists. As genomic characterization of the disease has progressed over the past two decades, there is increasing recognition of distinct genotypes that yield unique phenotypes **(Chap. 283)**, such as the demonstration of a primarily fibrotic endophenotype governed by the (oxidized) scaffold protein NEDD-9 and its aldosterone-dependent, TGF-β-independent enhancement of collagen III expression. This approach will continue to evolve as therapies become more effective (e.g., for perivascular fibrosis) and therapeutic choices better targeted to individual patients.

Precision genomics has also led to a new classification of the dementias, conditions previously thought to have a single cause with varied clinical expression. These disorders can now be categorized based on the genes and pathways involved and the site where aggregated proteins first form and then spread in the nervous system. For example, the varied clinical presentations of frontotemporal dementia, including progressive aphasia, behavioral disturbances, and dementia with amyotrophic lateral sclerosis, can now be linked to specific genotypes and susceptible cells **(Chap. 432)**. In prion diseases, the clinical phenotype is determined by specific germline mutations present in the prion protein **(Chap. 438)**. Discovery of autoantibodies against aquaporin-4 (AQP-4) and myelin oligodendrocyte glycoprotein (MOG) has allowed neuromyelitis optica, previously considered a multiple sclerosis–like disorder, to be classified as a separate entity requiring different treatment **(Chap. 445)**. Similarly, in myasthenia gravis, the identification of novel autoantibodies now permits stratification and a more finely tuned precision approach to therapy **(Chap. 448)**.

Precision medicine approaches to cancers have, of course, become the prime example of the opportunity that this strategy offers. In the pregenomic era, chemotherapy was widely used with variable success despite continued efforts to characterize the molecular features of the specific tumors and their semi-empiric responses to specific chemotherapeutic agents. As cancer genome sequencing evolved, however, it became apparent that there are a limited number of oncogenic pathways (<20) that are represented in the great majority of malignancies, without regard for the organ in which the disease was primarily manifest. These genomic signatures served as a template for precisely targeted therapies that have led to dramatic changes in response to treatment, including, for example, imatinib (and congeners) for Bcr-Abl tyrosine kinase activity in chronic myelogenous leukemia, erlotinib for *EGFR*-mutant non-small cell lung cancers, and ibrutinib for Bruton tyrosine kinase in chronic lymphocytic leukemia, among many others.

As exciting as these approaches have been, there are at least three primary challenges associated with precision therapeutics that are unique to cancer: (1) the mutational landscape continues to evolve as the disease progresses, and therapy often (if not invariably) leads to selection for resistant clones; (2) the likelihood that any cancer can be definitively cured by any single agent, no matter its exquisite precision, is quite limited, necessitating the development of rational polypharmaceutical approaches that take into account alternative pathways that achieve the same oncogenic goals as the primary targeted pathway, complicating drug development; and (3) there is marked genomic heterogeneity in many malignancies arguing that targeting a specific pathway—even with multiple drugs—may not ultimately succeed over the long term owing to the continued and heterogeneous evolution of the genomic landscape within a tumor within a patient. Despite these serious shortcomings, the application of progressively more refined and precisely targeted therapies used alone and in combination, such as with immune modulators, continues to offer great promise for the treatment of these diseases. In some ways, these approaches in cancer mirror earlier strategies in the treatment of infectious diseases in which the identification of the causative organism and its sensitivity to potential antimicrobials allows precision approaches to treatment. Combinatorial antimicrobial treatments represent an effective strategy to address acquired resistance. These diagnostic and therapeutic strategies can be applied without detailed knowledge of personalized responses to the infection or treatment (aside from serious adverse effects) with good outcomes in most cases. Yet, individuals do respond differently to specific infections and their treatments, possibly driven by different endophenotypes (e.g., different inflammatory responses), suggesting that more precise knowledge of these precise mechanistic differences may yield improved prognosis and therapeutic approaches. As with cancer, immune modulation, particularly for immune exhaustion in chronic infections, represents a new frontier, again amenable to the personalized, precise analyses described above.

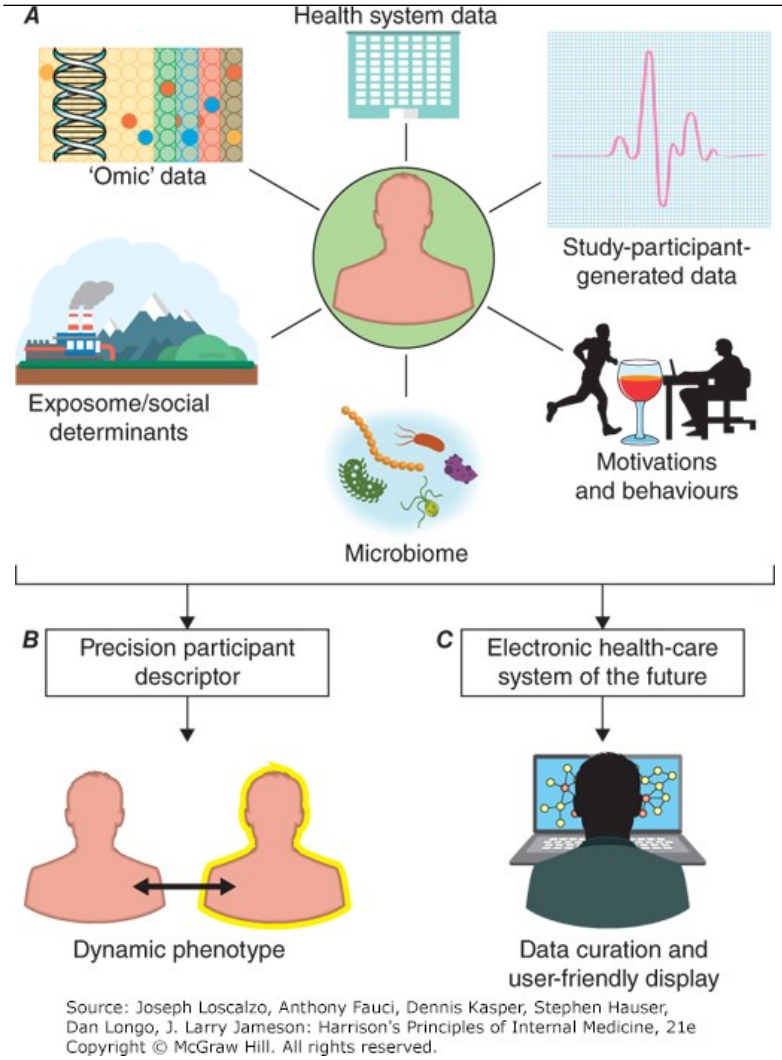
THE FUTURE OF PRECISION MEDICINE

Precision medicine clearly holds great promise for the future of the practice of medicine. For precision medicine to continue to evolve successfully, however, several requirements will need to be met. First, both deeply refined personal phenotypic data and genomic data are essential as the information with which precision analysis is performed. These data sets are quite large and require sufficient storage for analysis, especially for individuals in whom time trajectories are acquired (as should be the case for every person). Equally important, the analytical methods required to extract useful information from these data sets are evolving and themselves quite complex. While great progress has been made in genomics and biochemical testing, our ability to capture meaningful immunologic endophenotypes and environmental exposures is limited by comparison. Machine learning and artificial (auxiliary) intelligence methods will be essential for extracting optimal information from these data sets, which include not only pathways that can be uniquely targeted therapeutically but also individualized genomic or phenotypic signatures that are highly predictive of outcome, with or without therapy. Gathering sufficient information on the "normal" segments of the population is also required to ensure appropriate comparison data sets for optimal prediction.

Second, phenotyping must continue to expand and become dimensionally richer. The phenotypic features included in this data gathering must incorporate not only data relevant to the clinical presentation but also orthogonal phenotypic data that may yield useful information on disease trajectory or preclinical disease markers. Personal device data, environmental exposure history, social network interactions, and health system data will all be incorporated increasingly in defining phenotype and will require great efforts on the part of the medical informatics community to harmonize data sets, standardize data collection, and optimize/standardize data analysis **(Fig. 5-7)**.

FIGURE 5-7

Big data in precision medicine. ***A.*** Six dimensions by which individuals may be characterized in the precision medicine era are described. ***B.*** The precision participant descriptor integrates the data from these six dimensions and varies over time. ***C.*** The electronic medical record increasingly must evolve to provide curated precision data in a user-friendly way. *(Reproduced with permission from EM Antman, J Loscalzo: Precision medicine in cardiology. Nat Rev Cardiol 13:591, 2016.)*



Source: Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson: Harrison's Principles of Internal Medicine, 21e

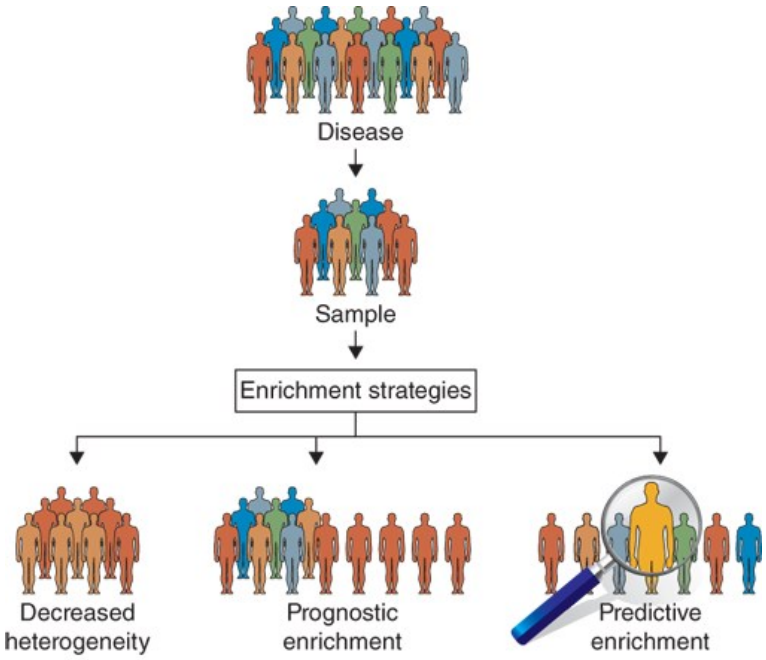
Third, perhaps the greatest challenge to making precision medicine the standard approach to illness will be to determine the minimal data set required to predict outcome and response to therapy. Gathering data is comparatively simple; however, analyzing it to eliminate redundant information in these overdetermined biologic systems, weighting the determinants of an outcome, and using the data as phenomic/genomic signatures that are easier to collect than comprehensive, unbiased data sets are the ideal goals—a major challenge, but not insurmountable. Rapidly evolving machine learning and artificial intelligence strategies will also be essential for maximal success.

To return to the question of how precise precision medicine needs to be in order to be useful, please refer to **Fig. 5-8** where the approaches to clinical trial design meant to improve therapeutic signal are illustrated. Decreasing heterogeneity and enriching the study population will enhance the effect size, but these strategies are based on analyses of prior data sets that define those individuals who are more likely than not to respond to a therapy. By contrast, the notion of predictive enrichment follows from the information provided by a detailed, big data–driven analysis of individuals that explores phenotypic and genomic features used to predict response. These features need not be precisely met by each patient; however, they can be collated or clustered to define a reasonably sized cohort predicted to respond in a particular way within certain confidence bounds. In this way, the boundaries to the practice of precision medicine are imprecise strictly speaking, but sufficiently predictive to be practical from the perspectives of clinical care and cost-effectiveness.

FIGURE 5-8

The basis for precision medicine. The notion of precision medicine evolved, in part, from clinical trial design. From the entire population of patients with the disease of interest, a sample cohort of individuals is enrolled in the trial that ideally is representative of the entire distribution. Enrichment strategies developed to decrease heterogeneity or increase the representation of individuals with a high risk of observed outcomes

(prognostic enrichment) facilitate trial conduct but do not necessarily improve precision in defining treatment response. The predictive enrichment strategy utilizes both trial participant characteristics and data from experiments conducted before or during (adaptive design) the trial to improve the prediction of who is likely to have a more pronounced response to the treatment under study. *(Reproduced with permission from EM Antman, J Loscalzo: Precision medicine in cardiology. Nat Rev Cardiol 13:591, 2016.)*



FURTHER READING

Antman EM, Loscalzo J: Precision medicine in cardiology. Nat Rev Cardiol 13:591, 2016. [PubMed: 27356875]

Cheng F et al: Comprehensive characterization of protein-protein interactions perturbed by disease mutations. Nat Genet 53:342, 2021. [PubMed: 33558758]

Cheng F et al: A genome-wide positioning systems network algorithm for in silico drug repurposing. Nat Commun 10:3476, 2019. [PubMed: 31375661]

Greene JA, Loscalzo J: Putting the patient back together—Social medicine, network medicine, and the limits of reductionism. N Engl J Med 377:2493, 2017. [PubMed: 29262277]

Kitsak M et al: Tissue specificity of human disease module. Sci Rep 6:35241, 2016. [PubMed: 27748412]

Lee LY, Loscalzo J: Network medicine in pathobiology. Am J Pathol 189:1311, 2019. [PubMed: 31014954]

Leopold JA et al: The application of big data to cardiovascular disease: Paths to precision medicine. J Clin Invest 130:29, 2020. [PubMed: 31895052]

Loscalzo J et al: Human disease classification in the postgenomic era: A complex systems approach to human pathobiology. Mol Syst Biol 3:124, 2007. [PubMed: 17625512]

Maron BA et al: Individualized interactomes for network-based precision medicine in hypertrophic cardiomyopathy with implications for other clinical pathophenotypes. Nat Commun 12:873, 2021. [PubMed: 33558530]

Menche J et al: Disease networks. Uncovering disease-disease relationships through the incomplete interactome. Science 347:1257601, 2015. [PubMed: 25700523]

Samokhin AO et al: NEDD9 targets *COL3A1* to promote endothelial fibrosis and pulmonary arterial hypertension. Sci Transl Med 10:eaap7294, 2018. [PubMed: 29899023]