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Strategic vision for improving human health at The Forefront of Genomics

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Starting with the launch of the Human Genome Project three decades ago, and continuing after its completion in 2003, genomics has progressively come to have a central and catalytic role in basic and translational research. In addition, studies increasingly demonstrate how genomic information can be effectively used in clinical care. In the future, the anticipated advances in technology development, biological insights, and clinical applications (among others) will lead to more widespread integration of genomics into almost all areas of biomedical research, the adoption of genomics into mainstream medical and public-health practices, and an increasing relevance of genomics for everyday life. On behalf of the research community, the National Human Genome Research Institute recently completed a multi-year process of strategic engagement to identify future research priorities and opportunities in human genomics, with an emphasis on health applications. Here we describe the highest-priority elements envisioned for the cutting-edge of human genomics going forward—that is, at 'The Forefront of Genomics'.

Beginning in October 1990, a pioneering group of international researchers began an audacious journey to generate the first map and sequence of the human genome, marking the start of a 13-year odyssey called the Human Genome Project[1–3]. The successful and early completion of the Project in 2003, which included parallel studies of a set of model organism genomes, catalysed enormous progress in genomics research. Leading the signature advances has been a greater than one million-fold reduction in the cost of DNA sequencing[4]. This decrease has allowed the generation of innumerable genome sequences, including hundreds of thousands of human genome sequences (both in research and clinical settings), and the continuous development of assays to identify and characterize functional genomic elements[5,6]. These new tools, together with increasingly sophisticated statistical and computational methods, have enabled researchers to create rich catalogues of human genomic variants[7,8], to gain an ever-deepening understanding of the functional complexities of the human genome[5], and to determine the genomic bases of thousands of human diseases[9,10]. In turn, the past decade has brought the initial realization of genomic medicine[11], as research successes have been converted into powerful tools for use in healthcare, including somatic genome analysis for cancer (enabling development of targeted therapeutic agents)[12], non-invasive prenatal genetic screening[13], and genomics-based tests for a growing set of paediatric conditions and rare disorders[14], among others.

In essence, with growing insights about the structure and function of the human genome and ever-improving laboratory and computational technologies, genomics has become increasingly woven into the fabric of biomedical research, medical practice, and society. The scope, scale, and pace of genomic advances so far were nearly unimaginable when the Human Genome Project began; even today, such advances are yielding scientific and clinical opportunities beyond our initial expectations, with many more anticipated in the next decade.

Embracing its leadership role in genomics, the National Human Genome Research Institute (NHGRI) has developed strategic visions for the field at key inflection points, in particular at the end of the Human Genome Project in 2003[15] and then again at the beginning of the last decade in 2011[16]. These visions outlined the most compelling opportunities for human genomics research, in each case informed by a multi-year engagement process. NHGRI endeavoured to start the new decade with an updated strategic vision for human genomics research. Through a planning process that involved more than 50 events (such as dedicated workshops, conference sessions, and webinars) over the past two years (see http://genome.gov/genomics2020), the institute collected input from a large number of stakeholders, with the resulting input catalogued and synthesized using the framework depicted in Fig. 1.

Unlike the past, this round of strategic planning was greatly influenced by the now widely disseminated nature of genomics across biomedicine. A representative glimpse into this historic phenomenon is illustrated in Fig. 2. During the Human Genome Project, NHGRI was the primary funder of human genomics research at the US National Institutes of Health (NIH), but the past two decades have brought a greater than tenfold increase in the relative fraction of funding coming from other parts of the NIH.

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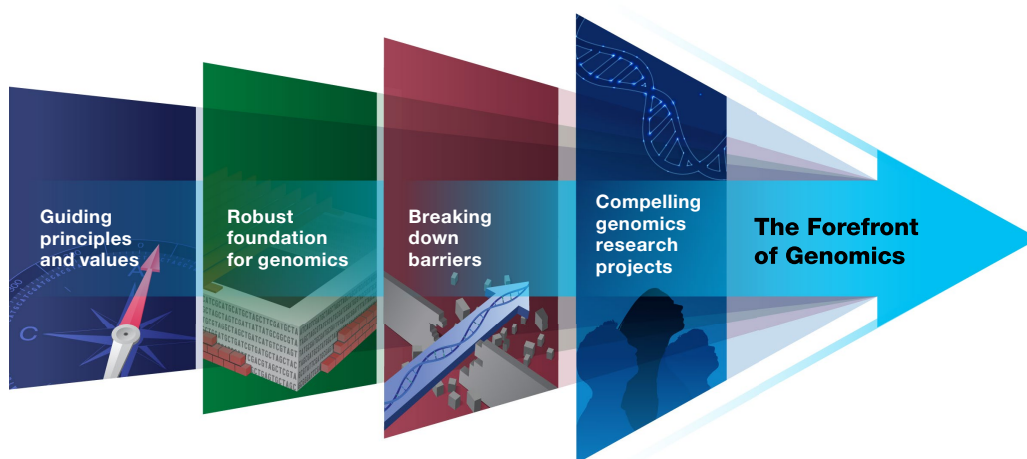
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The planning process continually encountered the realities associated with the broad and extensive use of genomics and the impracticality of being comprehensive, which together served to focus attention on the most cutting-edge opportunities in human genomics. This experience affirmed NHGRI's recently rearticulated role in providing genomics leadership at the NIH, embodied by our newly conceived organizational mantra: 'The Forefront of Genomics'. We ultimately linked this mantra to the strategic planning process to help guide the formulation of input. From the ensuing discussions, it became apparent that responsible stewardship is a central aspect of being at (and pushing forward) The Forefront of Genomics, specifically in the four major areas detailed in Fig. 1, Boxes 1–4, and below.

Principles and values for human genomics

As genomics has matured as a discipline, the field has embraced a growing set of fundamental principles and values that together serve as a guiding compass for the research efforts—some of these emerged organically within the field, whereas others have been adopted from the broader scientific community. The growing complexities of human genomics and its many applications (especially in medicine) at The Forefront of Genomics make it imperative to reaffirm, sharpen, and even extend these tenets, such as those highlighted in Box 1.

Many of these principles and values have been informed by the recognized area of genomics that focuses on ethical, legal, and social implications (ELSI) research[17], which was established at the beginning of the Human Genome Project to ensure that the eugenics movement and other misuses of genetics are not repeated. ELSI research has since grown to encompass a broad portfolio of studies that examine issues at the interface of genomics and society, the results of which have informed policies and laws related to genetic discrimination, intellectual property, data sharing, and informed consent[18]. Similar efforts seek to ensure that the benefits of genomics are available to all members of society[19]. Genomics, like other scientific fields, must reckon with systematic injustices and biases, fully mindful of their importance for health equity. In the future, ELSI research needs to focus on aspects of genomic medicine implementation that present challenging questions about legal boundaries, study governance, data control, privacy, and consent. Complex societal issues must also be studied, including the expanded application of genomics in non-medical realms (for example, ancestry testing, law enforcement, and genetics-based marketing of consumer goods)[20]. Finally, ELSI research should also examine the implications of studying genetic associations with bio-behavioural traits (such as intelligence, sexual behaviour, social status, and educational attainment)[21] and of a future in which machine learning and artificial intelligence are used to adapt risk communication and clinical decisions based on analysing an individual's genome sequence[22].

Robust foundation for genomics

Genomics is now routinely and broadly used throughout biomedical research, with widespread reliance on a robust foundation for facilitating genomic advances. The foundation's integrity depends on several key elements, including infrastructure, resources, and dynamic areas of technology development and research. Sustaining and improving that foundation are key responsibilities at The Forefront of Genomics,

NIH funding

NHGRI funding

Proportion of 'human genomics' funding

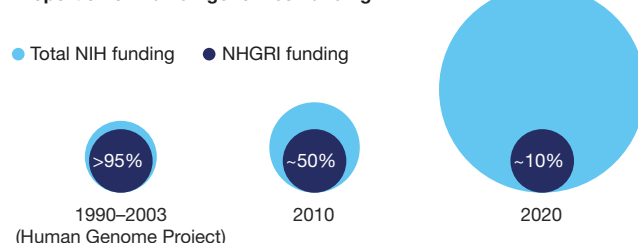- Total NIH funding
- NHGRI funding

Fig. 2 | Funding trends of NIH and NHGRI over the past 30 years. The total funding levels for the NIH (top) and NHGRI (middle) are indicated for 1990, 2010, and 2020. Also shown (bottom) is the relative proportion of funds supporting human genomics research provided by NHGRI versus all of the NIH for the three corresponding time intervals (as derived from queries of the internal NIH Research, Condition, and Disease Categorization database for funds assigned to the 'human genome' category). During the 30-year period when the NHGRI budget increased roughly tenfold (middle), the proportion of total NIH funding for human genomics research actually increased more markedly, from less than 5% during the Human Genome Project to around 90% at the beginning of the current decade (bottom). In essence, these trends reflect a leveraging of NHGRI's funds that increased NIH's overall human genomics research funding by greater than tenfold.

Box 1

Guiding principles and values for human genomics

- **Maintain an overarching focus on using genomics to understand biology, to enhance knowledge about disease, and to improve human health** — genomics is now foundational across the entire continuum of biomedical research, from deciphering fundamental principles of biology to translating that knowledge into disease prevention and medical advances.
- **Strive for global diversity in all aspects of genomics research, committing to the systematic inclusion of ancestrally diverse and underrepresented individuals in major genomic studies** — attention to diversity in genomics research is both socially just and scientifically essential, which includes meaningful, sustained partnerships with diverse communities in the design and implementation of research studies, the propagation of research findings, and the development and use of new technologies.
- **Maximize the usability of genomics for all members of the public, including the ability to access genomics in healthcare** — engagement, inclusion, and understanding the needs of diverse and medically underserved groups are required to ensure that all members of society benefit equitably from genomic advances, with particular attention given to the equitable use of genomics in healthcare that avoids exacerbating and strives towards reducing health disparities.
- **Champion a diverse genomics workforce** — the promise of genomics cannot be fully achieved without attracting, developing, and retaining a diverse workforce, which includes individuals from groups that are currently underrepresented in the genomics enterprise.
- **Provide a conceptual research framing that consistently examines the role of both genomic and non-genomic contributors to health and disease** — routinely considering the importance of social and environmental factors that influence human health (and the interactions among those components and genomics) will be important for the comprehensive understanding of most human diseases.
- **Promote robust and consistently applied standards in genomics research** — the use of carefully defined standards (for example, those for generating, analysing, storing, and sharing data) has benefited genomics in numerous ways, and this must include appropriate privacy and data-security protections for those participating in genomics research.
- **Embrace the interdisciplinary and team-oriented nature of genomics research** — starting with the Human Genome Project, some of the most challenging genomics endeavours have benefited from the creation and management of large, interdisciplinary research collaborations.
- **Adhere to the highest expectations and requirements related to open science, responsible data sharing, and rigor and reproducibility in genomics research** — the genomics enterprise has a well-respected history of leading in these areas, and that commitment must be built upon and continually reaffirmed.
- **Pursue advances in genomics as part of a vibrant global community of genomics researchers and funders** — the challenges in genomics require the collective energies and creativity of a collaborative international ecosystem that includes partnerships among researchers, funders, and other stakeholders from academia, government, and the commercial sector.

the major elements of which are highlighted in Box 2 and detailed in corresponding paragraphs below.

Genome structure and function

The past two decades have brought a greater than million-fold reduction in the cost of DNA sequencing[23] along with marked advances in technologies for functional genomics[6,24,25] (that is, the study of how elements in the genome contribute to biological processes). Further opportunities are anticipated as the generation and analysis of genomic data become even faster, cheaper, and more accurate. Near-term expectations include enhanced capabilities for generating high-quality and complete (for example, telomere-to-telomere and phased) genome sequences[26,27], and continued refinement and enhanced utilization of a human genome reference sequence(s) that increasingly reflects human variation and diversity on a global scale[28] and that serves as a substrate for genome annotation[29]. Technologies for generating DNA sequence and other data types (for example, transcriptomic data, epigenetic data, and functional readouts of DNA sequences) need to be enabled at orders-of-magnitude lower costs, at single-cell resolution, at distinct spatial locations within tissues, and longitudinally over time[30–32]. These genomic data should be integrated with other multi-omic data (for example, proteomes, metabolomes, lipidomes, and/or microbiomes) in sophisticated ways, including methods that collect many data types from a single sample[32]. Transformative approaches will become increasingly vital for assimilating, sharing, and analysing these complex and heterogeneous data types[33] and must expand to include the integration of environmental, lifestyle, clinical, and other phenotypic data. These capabilities should be incorporated into browsers, portals, and visualization tools for use by a broadening community of researchers and clinicians.

Genome sequences have now been generated for more than 1,000 vertebrate species and are increasingly accompanied by multi-species annotations[34]. Understanding natural genomic variation, the conservation of genomic elements, and the rapid evolutionary changes in genomic regions associated with specific traits is crucial for attaining a comprehensive view of genome structure and function. The study of a wide range of organisms continues to be instrumental for determining the effect of genomic variation on biological processes and phenotypes, providing insights about the interplay of genomic variants and environmental pressures[35] and the relevance of putative pathogenic variants identified in clinical studies[36]. It is essential that the generation of high-quality multi-species genomic data is accompanied by community-accepted standards for data, metadata, and data interoperability. New methods would allow for integrating functional data from diverse species with human data and visualizing increasingly complex comparative genomic datasets. Continued progress in this area would move the field closer to the long-term aspirational goal of understanding the evolutionary history of every base in the human genome.

Genomic data science

All major genomics breakthroughs so far have been accompanied by the development of ground-breaking statistical and computational methods. Accordingly, continued innovations in both traditional and advanced methods (including machine learning and artificial intelligence) should be prioritized[37]. These approaches must be considered from the early stages of study planning and data collection in ways that complement and enhance, rather than inhibit, technical progress. Furthermore, the biomedical research community requires accurate, curated, accessible, secure, and interoperable genomic data

Box 2

Sustaining and improving a robust foundation for genomics

Genome structure and function
- Enable the routine generation and analysis of increasingly complex genomic data
- Use evolutionary and comparative genomic data to maximize understanding of genome function

Genomic data science
- Develop new methods and build sustainable data resources for genomics research
- Ensure facile storing, sharing, and computing on large genomic datasets
- Develop integrated knowledgebases and informatics methods for genomic medicine

Genomics and society
- Understand the interrelationships between genomics and the social and environmental factors that influence human health
- Empower people to make well-informed decisions about genomic data and develop data-stewardship systems that reinforce their choices
- Increase the genomic literacy of all sectors of society

Training and genomics workforce development
- Ensure that the next generation of genomic scientists are sufficiently trained in data science
- Train healthcare providers to integrate genomics into the clinical workflow
- Foster a diverse genomics workforce
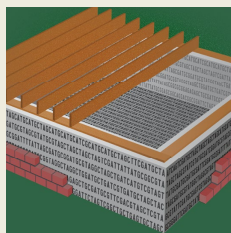
repositories and informatics platforms that benefit all populations. Approaches for improving the efficiency of such resources include the use of shared storage and computing infrastructure, the adoption of common data-management processes, and the development of increasingly automated data-curation methods[38]. Carefully considered funding strategies must be designed to support these methods and resources, including a global, multi-funder model that ensures their development, enhancements, and long-term sustainability[39].

Recent progress has brought substantial transformations in how the petabytes of genomic data being generated each year are assimilated and analysed, including the emergence of cloud-based and federated approaches. Effective and efficient management of increasingly complex genomic datasets requires addressing challenges with these emerging approaches as well as innovations in the use of hardware, algorithms, software, standards, and platforms[40]. Current barriers include the lack of interoperable genomic data resources (which limits downstream access, integration, and analyses) and the absence of controlled and consistently adopted data and metadata vocabularies and ontologies[41,42]. User-friendly systems that capture metadata in a scalable, intelligent, and cost-effective manner and that allow for intuitive data visualizations are essential. Ever-improving routines and guidelines should be formulated to continue and even enhance responsible data sharing, requiring the collective efforts of researchers, funders, and publishers alike; similar attention should focus on ensuring the use of FAIR (findable, accessible, interoperable, and reusable) data standards and the reproducibility of data analyses[38]. Innovations in technology and policy must be integrated to develop data-stewardship models that ensure open science and reduce data-access burdens to advance research, including the use of optimally balanced and ethically sound approaches for respecting participant

preferences and consent as well as engaging communities. Such developments should be done in an open-source culture to build consensus and enable the development, maintenance, and use of best-in-class tools, pipelines, and platforms that can be applied to all datasets.

The full integration of genomics into medical practice will require informatics and data-science advances that effectively connect the growing body of genomic knowledge to clinical decision-making. To make genomic information readily accessible and broadly useful to clinicians, user-friendly electronic health record-based clinical decision support tools must be created to interact with a variety of clinical data from electronic health record and other data systems (for example, laboratory, pharmacy, and radiology) as well as non-computable reports, such as those provided as portable document format (PDF) files[43,44]. These efforts require well-curated, highly integrated, and up-to-date knowledgebases that connect genomic information to clinical characteristics, other phenotypic data, and information on family health history[45]. Reliable risk-stratification and prevention algorithms, including polygenic risk scores (PRSs)[46], must be developed and should incorporate both common and rare genomic variants from a broad range of population subgroups, phenotypic data, and environmental information into the risk modelling[47]. Such algorithms should be evaluated both for their validity across many populations and for their effect on patient outcomes and subsequent healthcare utilization. Finally, it will be important to evaluate new genomics-oriented clinical decision support tools to ensure that they are acceptable to practitioners across the spectrum of clinical disciplines.

Genomics and society

Understanding the role of genomics in human health requires knowledge and insights about how social, environmental, and genomic risk factors interact to produce health outcomes[48,49] (Box 1). Given that such interactions are, in general, poorly understood, it is crucial that studies of genomic risk (particularly of common, complex diseases) account for the social and environmental factors that influence health and disease[50]. These factors must be properly described, measured, and incorporated in genomic studies[51]. Optimal implementation of genomic medicine will require an understanding of how the intersectional aspects of people's social and political identities influence the ways in which populations are described in research. Such knowledge will, in turn, provide clarity about the interrelationships among these many influences on health and disease.

People want to be able to make well-informed decisions about their genomic data, leading to the engagement efforts in initiatives such as the UK Biobank[52] and the 'All of Us' Research Program[53]. Partnering with communities and individuals is fundamental to engaging participants in such large-scale research. Genomics researchers must incorporate models and methods of community engagement in their experimental design. Such studies must be appropriately adapted for different cultures and designed to reduce inequities and healthcare disparities; they must also be accompanied by effective information dissemination[54]. An unrelenting focus on the optimal ways to conduct research in partnership with data stakeholders and communities would ensure the identification of the key issues and values influencing peoples' choices about the provision of personal data for research[55,56]. Data-stewardship infrastructures that integrate appropriate policies, technologies[57], and governance and legal frameworks must be developed and assessed to ensure alignment between communities' and individuals' decisions about their data and the practices of researchers and clinicians.

To fully realize the benefits of genomic advances, a working understanding of the basic concepts of genomics will be important for science educators[58], healthcare professionals[59], policymakers, and the public[60]. Several educational strategies will inevitably be required to enhance the genomic literacy of these heterogeneous groups, which points to the need for innovative approaches that are shared, assessed, and improved over time[58]. A growing evidence base shows that increasing the understanding

Breaking down barriers that impede progress in genomics

Laboratory and computational technologies

- Transform the study of the functional consequences of genomic variation by enhancing the scale of DNA synthesis and editing
- Maximally leverage the usability and utility of emerging datasets for genomic studies of human health and disease
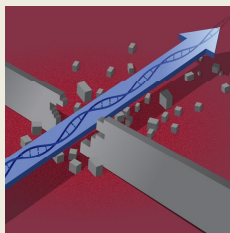
Biological insights

- Establish the means to determine the functional consequences of genomic variants affecting human health and disease
- Characterize intraindividual genomic variation and understand its role in human disease

Implementation science

- Develop and assess strategies for implementing the use of genomic information in clinical care
- Test public health approaches for implementing population-wide genomic screening

of key genomics concepts and applications attracts students to careers in genomics[61], assists with the use of genomics for addressing health disparities[62], and facilitates the uptake of genomic medicine[63]. Curricula for enhancing genomic literacy must be designed to be accessible, effective, and scalable for use in the full range of settings where genomics education is provided—including primary and secondary schools, science museums, and informal science-education venues. Researchers and educators must also disseminate information about both the science of genomics as well as the key ethical and societal implications of genomics[64].

Training and genomics workforce development

Appropriate skills in data science and data stewardship are now prerequisites for becoming a genomics researcher[65]. Furthermore, given the ever-expanding use of genomics in basic, translational, social, behavioural, and clinical research, a greater number of scientists will require fundamental data-science skills that are appropriate for the genomic applications being used[66]. Establishing and maintaining data-science competencies for conducting genomics research requires a series of interrelated educational and training efforts[67], including the recruitment of many data scientists into genomics and the reciprocal exchange of expertise between genomics researchers and data scientists.

Moving into healthcare, providers must be poised to manage questions from patients who receive genomic information, including that from direct-to-consumer (DTC) testing, and this applies to the full spectrum of medical professionals (including nurses, pharmacists, physicians, and other clinicians)[68]. Education modules tailored to specific user groups should be designed to adapt rapidly to advances in genomics and data-science technologies; these should be available on demand and, where appropriate, integrated into existing clinical systems[69]. Research on the methodologies for train-the-trainer approaches, implementation of standards and competency-based education, and strategies for enhancing genomic literacy among all healthcare providers at all career stages[70] should also be pursued. The involvement of patients, caregivers, educators, professional organizations[71], and accreditation boards will be crucial to ensure success. Importantly, cross-training in relevant aspects of genomics must also

be available for specialists working in or around healthcare systems, including (but not limited to) those involved in health services research, health economics, law, bioethics, and social and behavioural sciences.

In both research and clinical settings, the global genomics workforce—as with the general biomedical research workforce—falls considerably short of reflecting the diversity of the world's population (a vivid example of this is seen in the United States[72]), which limits the opportunity of those systematically excluded to bring their unique ideas to scientific and clinical research[73]. To attain a diverse genomics workforce, new strategies and programs to reduce impediments to career opportunities in genomics are required, as are creative approaches to promote workforce diversity, leadership in the field, and inclusion practices. Efforts must intentionally include women, underrepresented racial and ethnic groups, disadvantaged populations, and individuals with disabilities. Initiatives should not focus exclusively on early-stage recruitment; instead, they must also include incentives to recruit and retain a diverse workforce at all career stages[74] as well as new approaches for cultivating the next generation of genomics practitioners.

Breaking down barriers in genomics

Genomics has benefited enormously from the proactive identification of major obstacles impeding progress and the subsequent focused efforts to break down those barriers. Prototypic successes include the call for a '[US]$1,000 human genome sequence' after completion of the Human Genome Project[15] and proposed actions to facilitate genomic medicine implementation in 2011[16]; in these cases, both the risks of failure and the benefits of success were high. Once again, breaking down barriers, as highlighted in Box 3 and detailed below, would accelerate progress and create new research and clinical opportunities at The Forefront of Genomics.

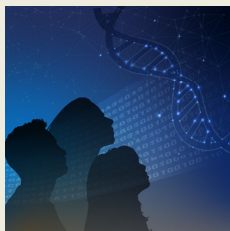## Laboratory and computational technologies

Advances in DNA synthesis and genome editing allow the field of genomics to progress from largely observational ('reading DNA') to more experimental ('writing' and 'editing' DNA) approaches. Enabling true 'synthetic genomics' (that is, the synthesis, modification, and perturbation of nucleic acid sequences at any scale) will allow for more powerful experimental testing of hypotheses about genome variation and function and improve opportunities for linking genotypes to phenotypes[75]. Genome editing is increasingly being used for practical applications in medicine (such as in gene therapy[76]), biotechnology, and agriculture. Despite recent triumphs, however, the current approaches are limited in their ability to interrogate genome function at the pathway or network level and to study important phenomena, such as gene regulation and chromosome organization and mechanics, that involve factors that act across large chromosomal (or genomic) distances. Furthermore, radically new capabilities for understanding how the full complement of genomic variation within any individual genome contributes to phenotype should be pursued. Innovative approaches for generating nucleic acid molecules with defined sequences and of any size, coupled with technologies that allow for the concurrent and large-scale perturbation of many genes or simultaneous examination of multiple genomic variants, would be transformative. These advances would benefit from the development of methods to introduce large synthetic constructs into mammalian cells.

In recent years, large human genomics projects have often relied on data generated as part of existing research studies, and emerging approaches involve developing biobanks and organized cohorts[77–79]. Meanwhile, DTC companies are generating substantial amounts of genomic data, and those efforts are rapidly being eclipsed by that being generated in the clinical care setting[80]. Properly leveraged, these DTC and clinical data offer opportunities for genomics-based studies at unprecedented scales; however, these data are often heavily fragmented, siloed, and mostly outside the purview of genomics researchers and their typical funders[81]. Eliminating the barriers to accessing these sources of data for conducting research is essential, but this will require resolving issues

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related to governance, policy infrastructure, and informatics and workflow solutions. Approaches are needed to mitigate the resulting gaps, limitations, and biases within this highly distributed data environment (for example, with regards to population diversity, data-collection strategies, data standards, and data privacy), all while addressing concerns of the patients, participants, and groups. These challenges must be addressed globally[81] (Box 1), so as to accommodate differences in healthcare systems and views about data privacy. In addition, the healthcare stakeholders should take advantage of opportunities offered by genomics, thereby enabling virtuous-cycle routes between genomic learning healthcare systems and basic genomics research[82] (Fig. 3).

Biological insights

Despite progress in identifying genomic variants that cause monogenic traits or are statistically associated with complex phenotypes, determining the connection of specific variants to phenotypes remains challenging[83]. Systematic approaches, including tactics that connect high-throughput molecular readouts of functional genomic assays to organismal phenotypes, are required to establish the phenotypic consequences of all genomic variants—individually and in combination—in a cell-type context across the life span[84]. Progress in this area requires global collaboration[85], advances in integrating several data types and performing perturbation assays, protein localization or interaction experiments, and animal models, as well as resources cataloguing information about the fitness consequences of de novo mutations and the clinical relevance of genomic variants[83]. Because it is not possible to directly test every variant in all cell types and states, developmental stages, and disease processes, new data-collection strategies and analytical approaches are needed that can generalize and adapt predictions to new contexts, handle sparse data, and prioritize variants for experimental follow-up.

Recent advances have led to a greater appreciation of the extent of mosaicism—that is, genomic variation among cells (both somatic and germline) within an individual. Although there have been remarkable advances in understanding the somatic genomic changes encountered in cancer[86], there is a paucity of detailed knowledge about other effects of mosaicism beyond a few well-studied examples[87]. Important areas of future research include investigating the prevalence and extent of different forms of mosaic variation in both nuclear and mitochondrial DNA, the mechanisms that generate mosaicism, and the roles of mosaicism in physiology and human disease. Such efforts might reveal whether this form of genomic variation contributes to variable penetrance and expressivity, comprises a form of genetic epistasis, explains any currently undiagnosed diseases or sporadic cases (or apparent phenocopies) of known inherited diseases[9], or can inform the design of therapies for genetic diseases. Single-cell genomic technologies have extended knowledge about the functional effects of mosaicism in different experimental systems[88,89], with the next challenge being to translate such single-cell understanding to in vivo settings. The development of laboratory and clinical approaches to readily detect genomic mosaicism at high spatial and temporal resolutions, especially in non-invasive ways (for example, requiring minimal amounts of tissue), would be catalytic.

Implementation science

A crucial barrier to using genomics for improving health and preventing disease is the lack of clinical uptake of proven genomic interventions. Implementation science approaches are needed to identify the most effective methods and strategies for facilitating the use of evidence-based genomic applications, most notably pharmacogenomics-based selection of medications[90], in routine clinical care. New experimental designs, such as genotype-specific participant recruitment[91] or integration of patient-provided genomic data[92] (captured during previous healthcare encounters or from DTC sources), should be explored for their potential to speed adoption and limit costs. The effectiveness of centralized resources for genomic referrals (for example, genomic medicine specialists, consult services[93,94], and centres of excellence in undiagnosed diseases—akin to transplantation centres or cancer centres) should be explored as potential steppingstones to the more generalized uptake of genomics in clinical care. Strategies for deploying the limited workforce of highly trained genetics or genomics specialists (for example, systematic referral networks or telemedicine or telecounseling) should also be evaluated for their effectiveness at increasing the availability of services broadly—as opposed to being limited to select, highly specialized centres.

Universal newborn genetic screening may represent the most visible and successful approach to population-based identification of serious and treatable inherited conditions, but population screening across the lifespan for other genetic conditions is less widely accepted. Standard public health screening approaches for the US Centers for Disease Control and Prevention Tier 1 conditions[95,96] (for example, Lynch syndrome, hereditary breast and ovarian cancer, and familial hypercholesterolemia) identify people at risk through blood relatives of affected individuals (referred to as 'cascade testing' by geneticists[97]). Implementation research methods, coupled with effective science communication, are primed for optimizing approaches to engage individuals in genetic testing for these disorders, in addition to other emerging indications, such as genetic predisposition to adverse drug effects (pharmacogenomics), carrier testing of prospective parents, use of PRSs in disease detection and prevention[46], and genomic indicators (for example, gene-expression and epigenetic patterns) of exposure to infectious pathogens[98] and other environmental agents.

Compelling genomics research projects

The field of genomics has routinely benefited from a willingness to articulate ambitious—often audacious—research efforts that aim to address questions and acquire knowledge that (at the time) may seem out of reach. Such boldness has served to stimulate interest in emerging opportunities, recruit new expertise, galvanize international collaborations involving several funders, and propel the field forward. Although by no means comprehensive, the areas highlighted in Box 4 and detailed below illustrate the broadening range of compelling research projects that are ripe for pursuit at The Forefront of Genomics.

Advances in understanding gene regulation[5,24], the myriad functional roles of RNA[99], and the multi-dimensional nature of the nucleome[100]—coupled with the use of single-cell genomic approaches[30,31] and anticipated
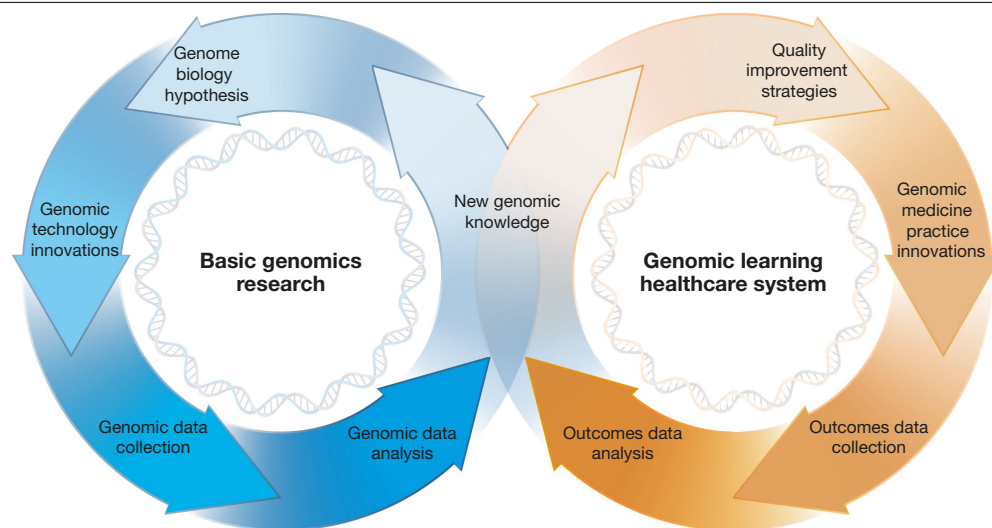
Fig. 3 | Virtuous cycles in human genomics research and clinical care.
As human genomics has matured as a discipline, productive and connected virtuous cycles of activity have emerged, each self-improving with successive rounds of new advances. The cycle on the left reflects basic genomics research, in which technology innovations spur the collection and analysis of genomics research data, often yielding new knowledge and further hypotheses for testing. The cycle on the right reflects a genomic learning healthcare system, in which the implementation of new genomic medicine practice innovations allows for the collection and analysis of outcomes data, often yielding new genomic knowledge and additional genomics-based strategies for improving the quality of clinical care. Note that the new knowledge emerging from either the left or the right cycle has the potential to feed into the other, creating opportunities for 'bench to bedside' and 'bedside back to bench' progressions[82]—both of which are expected to grow in the coming decade.

new technological and computational capabilities for analysing genomic datasets and variants—provide an unprecedented opportunity to decipher the individual and combined roles of each gene and regulatory element. This must start with establishing the function of each human gene, including the phenotypic effects of human gene knockouts. Because genes and regulatory elements do not function in isolation, it is imperative to build robust experimental and computational models that deduce causal relationships and accurately predict cellular and organismal phenotypes using pathway and network models[101,102]. Analysis methods must address functional redundancy as well as the nearly boundless experimental space and complexity, including cell states and fates, temporal relationships, environmental conditions, and individual genetic background.

Building on the recent successes in unravelling the genetic underpinnings of rare and undiagnosed diseases[9], the field is poised to gain a more comprehensive understanding of the genetic architecture of all human diseases and traits[10,85]. However, myriad complexities can be anticipated. For example, any given genomic variant(s) may affect more than one disease or trait (that is, pleiotropy); can confer disease risk or reduce it; and can act additively, synergistically, and/or through intermediates. New methods to analyse data that account for human diversity[103], coupled with a growing clarity about genotype–phenotype relationships, must be developed to deduce associations and interactions among genomic variants and environmental factors, improve estimates of penetrance and expressivity, and enhance the clinical utility of genomic information for predicting risk, prognosis, treatment response, and, ultimately, clinical outcomes.

Prioritizing the generation of genomic and corresponding phenotypic data from ancestrally diverse participants is a scientific imperative[104] and essential for achieving equitable benefits from genomic advances[105] (Box 1). However, this is an area in which genomics has repeatedly fallen short[19], leading to missed opportunities for understanding genome structure and function, identifying variants conferring risk for common diseases[106], and implementing genomic medicine for the benefit of all[107–109]. Ideally, studies should be designed for different groups, adapted for local sensibilities and situations, and consistent in capturing key information beyond participants' ancestry (for example, the physical and social environments in which they live and receive healthcare[110]). Leveraging new insights from studies of diverse populations will require the development of robust methods for identifying signatures of natural selection, performing genotype imputation, mapping disease loci, characterizing genomic variant pathogenicity, and calculating PRSs[103,109]. Success in these efforts will yield a more-complete understanding of how the human genome functions in different environments and offer benefit to those participating in genomics research. Attaining the level of population diversity that will truly benefit all people requires bold scientific and community-based leadership, dedicated resources from funders, highly committed researchers, and effective partnerships that earn the trust of diverse groups of participants and their communities.

As genomics has grown in medicine and society, its potential to influence people's actions has also expanded. Increasingly, genomics has affected concepts of health, disease, responsibility, family, identity, and community, raising many important and changing questions. When and how is genomic information shared and communicated within families[111]? Will the identification of a strong genetic risk for a disease change a person's perception of their health or others' perception of that person? As some genetic risks are more common in certain identifiable populations, what role does group affiliation have in how risk is communicated and perceived, including potential group stigmatization? Research that catalogues, analyses, and measures the effect of genomics on individuals, families, and communities is important to provide a more informed context to avoid future misrepresentations, misunderstandings, and misuses of genomics[54]. Finally, researchers must appreciate how their own backgrounds and experiences shape their interpretations of genomic data[112].

Extending genomics research in clinical settings beyond DNA sequence to include other multi-omic data, together with clinical variables and outcomes, would advance understanding of disease onset and progression and may also prove important for drug-discovery efforts[113,114]. This would require tissue- and cell-specific analyses that integrate these data, providing real-time snapshots of biological and disease processes. For clinical applicability and adoption, these high-dimensional, multi-omic data should be integrated with clinical decision support tools and electronic health records. Ultimately, such efforts could reveal important relationships among genomic, environmental, and behavioural variation and facilitate a transition of

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Box 5

Bold predictions for human genomics by 2030

Some of the most impressive genomics achievements, when viewed in retrospect, could hardly have been imagined ten years earlier. Here are ten bold predictions for human genomics that might come true by 2030. Although most are unlikely to be fully attained, achieving one or more of these would require individuals to strive for something that currently seems out of reach. These predictions were crafted to be both inspirational and aspirational in nature, provoking discussions about what might be possible at The Forefront of Genomics in the coming decade.

1. Generating and analysing a complete human genome sequence will be routine for any research laboratory, becoming as straightforward as carrying out a DNA purification.

2. The biological function(s) of every human gene will be known; for non-coding elements in the human genome, such knowledge will be the rule rather than the exception.

3. The general features of the epigenetic landscape and transcriptional output will be routinely incorporated into predictive models of the effect of genotype on phenotype.

4. Research in human genomics will have moved beyond population descriptors based on historic social constructs such as race.

5. Studies that involve analyses of genome sequences and associated phenotypic information for millions of human participants will be regularly featured at school science fairs.

6. The regular use of genomic information will have transitioned from boutique to mainstream in all clinical settings, making genomic testing as routine as complete blood counts.

7. The clinical relevance of all encountered genomic variants will be readily predictable, rendering the diagnostic designation 'variant of uncertain significance (VUS)' obsolete.

8. An individual's complete genome sequence along with informative annotations will, if desired, be securely and readily accessible on their smartphone.

9. Individuals from ancestrally diverse backgrounds will benefit equitably from advances in human genomics.

10. Breakthrough discoveries will lead to curative therapies involving genomic modifications for dozens of genetic diseases.

the use of genomics in medicine from diagnosing and treating disease to maintaining health.

Sharp barriers between research and clinical care obstruct the virtuous cycle of moving scientific discoveries rapidly into clinical care and bringing clinical observations back to the research setting[82] (Fig. 3). Learning healthcare systems—in which real-time data on outcomes of healthcare delivery are accessed and used to enhance clinical practice—can lead to continuous care improvement, but only if the barriers between research and clinical care are reduced[115]. For example, offering genome sequencing to all members of a healthcare system, performed in conjunction with research and participant engagement and provided in real time[81], could help to assess the clinical utility of genomic information and may allow providers to improve disease diagnosis and management. System-wide implementation of such an experiment requires not only extensive patient and provider education, sophisticated informatics capabilities, and genomics-based clinical decision support, but also the development and evaluation of data security and privacy protections to ensure patient confidentiality[116]. Patients should be engaged in the design of such systems and informed at entry to them (and periodically thereafter), so as to be fully aware of the nature of the ongoing research

with their clinical data and the goals and potential risks of their participation[117]. Extending such studies across many healthcare systems should reveal common challenges and solutions[118,119], thereby enhancing the learning healthcare model for genomic medicine more broadly (Fig. 3).

Concluding thoughts

The dawn of genomics featured the launch of the Human Genome Project in October 1990[1]. Three decades later, the field has seen stunning technological advances and high-profile programmatic successes, which in turn have led to the widespread infusion of genomic methods and approaches across the life sciences and, increasingly, into medicine and society.

NHGRI has for the third time[15,16] since the Human Genome Project undergone an extensive horizon-scanning process to capture, synthesize, and articulate the most compelling strategic opportunities for the next phase of genomics—with particular attention to elements that are most relevant to human health. The now near-ubiquitous nature of genomics (including in the complex healthcare ecosystem) presented practical challenges for attaining a holistic assessment of the field. Another reality was that the NHGRI investment in genomics has now been multiplied many-fold by the seeding of human genomics throughout the broader research community. These changes reflect a continued maturation of both the field (in general) and NHGRI (more specifically), nicely aligning with the institute's evolving leadership role at The Forefront of Genomics.

Embracing that role, NHGRI formulated the strategic vision described here, which provides an optimistic outlook that the successes in human genomics over the past three decades will be amplified in the coming decade. Many of the details about what is needed to fulfil the promise of genomics have now come into focus. Major unsolved problems remain—among them determining the role for the vast majority of functional elements in the human genome (especially those outside of protein-coding regions), understanding the full spectrum of genomic variation (especially that implicated in human disease), developing data-science capabilities (especially those that keep pace with data generation), and improving healthcare through the implementation of genomic medicine (especially in the areas of prevention, diagnosis, and therapeutic development). The new decade also brings research questions related to the societal implications of genomics, including those related to social inequities, pointing to the continued importance of investigating the ethical, legal, and social issues related to genomics. But now more than ever, solutions to these problems seem to be within striking distance. Towards that end (and with the characteristic spirit of genomics audacity), we offer ten bold predictions of what might be realized in human genomics by 2030 (Box 5).

The strategic vision articulated here was crafted on behalf of the field of human genomics and emphasizes broad strategic goals as opposed to implementation tactics. The realization of these goals will require further planning in conjunction with the collective creativity, energies, and resources of the global community of scientists, funders, and research participants. NHGRI has taken some initial steps to implement this vision, although these will inevitably need to be adapted as advances occur and circumstances change. Indeed, the final words of this strategic vision were formulated as the world moved urgently to deal with the coronavirus disease 2019 (COVID-19) pandemic (see below), providing a vivid reminder of the need to be nimble and the importance of nurturing all parts of the research continuum—from basic to translational to clinical—for protecting public health and advancing medical science.

Despite the seismic changes seen in genomics since the inception of the field, the fundamental sense of curiosity, marvel, and purpose associated with genome science seems to be timeless. In concluding NHGRI's previous strategic vision[16]—published just under a decade ago —the then-envisioned opportunities and challenges were provided with "… a continuing sense of wonder, a continuing need for urgency, a continuing desire to balance ambition with reality, and a continuing responsibility

to protect individuals while maximizing the societal benefits of genomics…." With the 2020 strategic vision described here providing a thoughtful guide and with enduring feelings of wonder, urgency, ambition, and social consciousness providing unfettered momentum, we are ready to embark on the next exciting phase of the human genomics journey.

Epilogue: COVID-19 and genomics

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a global threat to public health at the end of the multi-year process that generated the above strategic vision. Nonetheless, the COVID-19 pandemic provides a potent lesson about how a tiny string of nucleic acids can wreak global havoc on humankind. Understanding the mechanisms involved in the transmission of the virus, viral invasion and clearance, as well as the highly variable and at times disastrous physiological responses to infection, are fertile grounds for genomics research. Genomics rapidly assumed crucial roles in COVID-19 research and clinical care in areas such as (1) the deployment of DNA- and RNA-sequencing technologies for diagnostics, tracking of viral isolates, and environmental monitoring; (2) the use of synthetic nucleic acid technologies for studying SARS-CoV-2 virulence and facilitating vaccine development; (3) the examination of how human genomic variation influences infectivity, disease severity, vaccine efficacy, and treatment response; (4) the adherence to principles and values related to open science, data sharing, and consortia-based collaborations; and (5) the provision of genomic data science tools to study COVID-19 pathophysiology. The growing adoption of genomic approaches and technologies into myriad aspects of the global response to the COVID-19 pandemic serves as another important and highly visible example of the integral and vital nature of genomics in modern research and medicine.

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