REVIEW

Translational genomics and precision medicine: Moving from the lab to the clinic

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Translational genomics aims to improve human health by building on discoveries made through genetics research and applying them in the clinical setting. This progress has been made possible by technological advances in genomics and analytics and by the digital revolution. Such advances should enable the development of prognostic markers, tailored interventions, and the design of prophylactic preventive approaches. We are at the cusp of predicting disease risk for some disorders by means of polygenic risk scores integrated with classical epidemiological risk factors. This should lead to better risk stratification and clinical decision-making. A deeper understanding of the link between genome-wide sequence and association with well-characterized phenotypes will empower the development of biomarkers to aid diagnosis, inform disease progression trajectories, and allow better targeting of treatments to those patients most likely to respond.

Progress in the field of human genetics has been accelerated by recent technological advances, which allow the genome-wide interrogation of individual and population-wide sequence variation. This has led to the identification of new variants for Mendelian disorders already affecting clinical care; for more common complex diseases, in which multiple genetic and environmental effects combine to increase disease risk, thousands of genetic susceptibility variants have been identified. Translation of these findings into improvements in healthcare will require moving from association signal discovery to functional interpretation of that signal, and ultimately to clinical treatment, facilitated by large-scale data generation; developing advanced computational tool kits to process the wealth of information; addressing ethical, legal, social, and economic considerations; and effectively integrating genomics into routine clinical practice.

The translation of improvements in genetic understanding to health care can be seen for some rare monogenic diseases in which precision medicine, defined as an approach to allow more accurate prediction of the groups of people who will benefit from a specific treatment or prevention strategy for a particular disease, is already being used clinically. For example, ivacaftor is a drug that acts at the cystic fibrosis transmembrane conductance regulator channel to alter activity and is licensed for use in the 4 to 5% of cystic fibrosis patients with specific gating mutations in the gene encoding the protein (*1*). Cancer research is using precision medicine to target therapies according to tumor mutations and has led the field in translating insights from genomics into a better understanding of the mechanisms of disease and new drug development. For example, genome sequencing coupled with multi-omics–based molecular profiling has led to the development of personalized interventions such as chimeric antigen receptor T cell (CAR-T) immunotherapy (*2*). For common diseases, which are caused by combinations of multiple genetic and environmental factors, progress has been slower. However, genetically driven approaches are now starting to emerge; for example, recent studies have identified variants influencing efficacy (*3*) and tolerance (*4*) of metformin, a first-line treatment for type 2 diabetes, and have the potential to affect patient care.

In this review, we focus on complex disease genetics and explore how genetic and genomic discoveries can fuel the translational pathway to improve human health (Fig. 1).

How can genetic studies translate into clinical application?

Precision medicine

One of the immediate clinical applications arising from studies of complex disease genetics is the improved targeting of available therapies to those most likely to respond, or avoidance of therapy in those likely to develop adverse events. Information on an individual's genetic makeup can be used to estimate their likelihood of developing disease and their likely benefit if targeted for preventive care, or aid in the selection of the best treatment for that individual. Genetic studies to inform precision medicine in the context of best treatment include both "pharmacogenomic" studies (the identification of genetic variants that influence drug pharmacokinetics) and genetic studies that strive to define disease "endotypes" that might reflect different underlying disease etiopathologies that lie under the same diagnostic umbrella but with different optimal treatment strategies.

Most common complex diseases exhibit a variable disease course and response to therapy; of the 10 best-selling drugs in the United States, between 4 and 25 patients are treated in order to achieve one patient with a good response (*5*). This is not only a burden on health resources, but also exposes those patients who are treated without achieving a clinically significant response to the risk of harm through development of adverse events or through delays in switching to alternative treatments that might achieve benefit. This illustrates the need to develop better ways to target therapies.

Initiatives in the United States (*6*) and Europe (*7*) have been established to drive forward the precision medicine agenda, but progress has been relatively slow. One limiting factor is the measurement of progression or treatment response, which is often based on clinical end points rather than biomarkers. Genetic studies can identify which components of the outcome measures are heritable, and therefore predictable, which may help in developing outcomes that are more objectively measured (*8*). A further challenge in identifying predictors of drug response is poor drug adherence, which is common in chronic complex diseases. At least one in four patients does not take medication as prescribed (*9*), and this degree of misclassification affects the power of genetic and other biomarker studies to identify predictors of response. Despite these challenges, some genetic markers of drug response are emerging, such as the associations of the human leukocyte antigen (HLA)-C*06:02 with biologic therapy response in psoriasis (*10*), and HLA-DRB1 with severity, mortality, and treatment response to biologic drugs in rheumatoid arthritis (*11*).

Future precision medicine studies will consider the impact of nonresponse and nonadherence in the context of both pharmacogenomic studies and the emerging recognition of disease endotypes across most common complex diseases. The use of biomarkers as outcome measures, rather than clinical end points, will provide objective measures of response that more closely reflect the underlying biological processes in each patient.

Functional genomics and new drug target discovery

Genome-wide association studies (GWAS) in complex diseases have been successful in identifying robust associations between specific sequence variants and the phenotypes of interest. Individually, these associations characteristically confer

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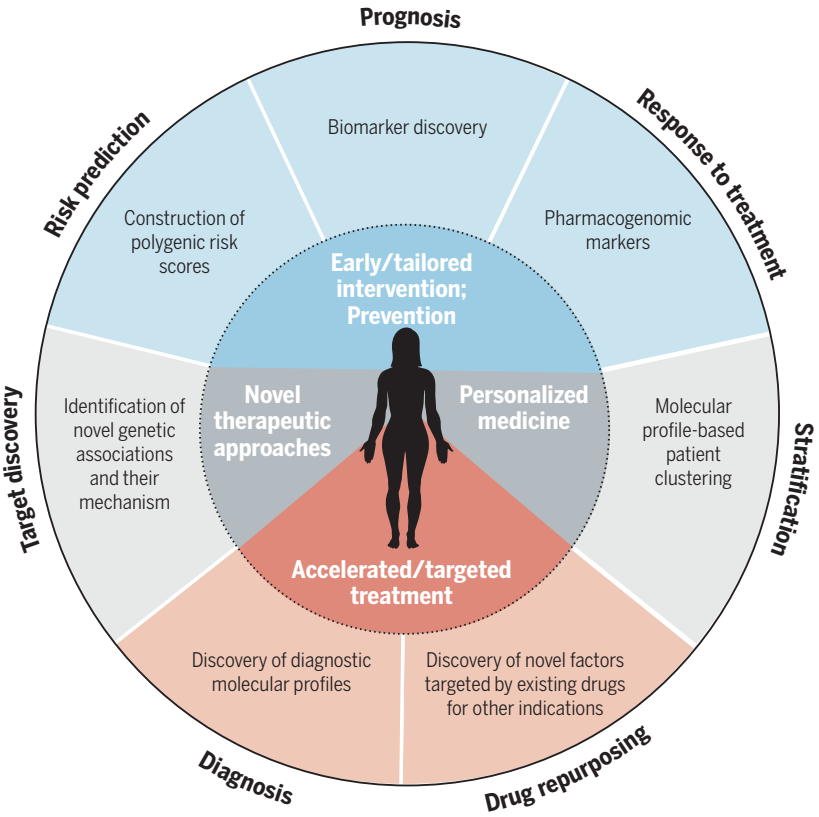


Fig. 1. The translational potential of complex disease genomics. Improvements to human health (inner circle) are achieved through various enabling milestones at different translational axes (outer circle).

modest to small effects, although there are notable exceptions, including the *HLA* alleles, which tend to exert large effects in autoimmune disease susceptibility in particular (*12*). In addition, rare or population-specific common variants have been associated with large effects on complex traits such as osteoarthritis (*13*) and type 2 diabetes (*14*). However, even if the genetic effect is small, it can be informative in terms of drug development pipelines; indeed, recent studies suggest that genes with underlying genetic support for an association with disease are twice as likely to encode successful drug targets in clinical development (*15*, *16*). Although the most widely described examples of drug targets with genetic support arise from familial rare disease studies, where rare variants with high penetrance and large effects result in disease (e.g., *PCSK9*) (*17*), GWAS signals increasingly implicate genes that encode known drug targets (Fig. 2). This provides retrospective proof of concept of the ability of GWAS to identify potentially new druggable targets. Furthermore, GWAS have identified drug-repurposing opportunities, i.e., targets for which there are already approved drugs, for other indications (*18*, *19*), which might be effective in treating an alternative disease.

The GWAS catalog currently contains ~138,000 genetic association signals with disease status or quantitative phenotypes from 4000 studies. Although each of these signals can act as a signpost to important genes and pathways, making the link between the signal and the specific gene(s) underlying the association has remained a major bottleneck. Although some signals very clearly implicate a particular gene, for example, through an experimentally validated functional amino acid change or introduction of a stop codon, the majority of genetic signals are either very broad, encompassing many variants across multiple genes, or are outside of gene regions entirely, suggesting a regulatory effect for which the target gene can be difficult to identify.

Computational (in silico) approaches can be used to map signals to effector genes; the availability of increasingly large sample sizes, deeply sequenced reference panels that allow variants not captured by genotype arrays to be imputed, and samples from ethnically diverse populations allow genetic association signals to be refined to smaller regions. However, it can still be challenging to determine which gene is being regulated and which variant is responsible. A genetic variant regulating gene expression may be functional and will likely reside in a region of open chromatin, but this may vary according to cell type and stimulatory condition. The increasing availability of multi-omics data, such as transcriptomics, proteomics, chromatin accessibility, and histone modifications, across multiple cell types and tissues and under different conditions, now facilitates advances in linking genetic signals to genes. International efforts such as the Genotype-Tissue Expression (GTEx) project, ENCODE, ROADMAP, and BLUEPRINT (*20*–*22*) have provided publicly available resources for studying tissue-specific gene expression and regulation, which can be leveraged to identify effector transcripts for GWAS signals (*23*). Interrogation of gene and protein expression data, annotation of epigenetic markers indicative of regulatory genomic regions, and chromosome interactions have identified potentially causal variants and genes for a large number of GWAS signals (Fig. 3). For example, in type 2 diabetes, functional annotation of genetically associated variants in human pancreatic islet cells enabled the fine-mapping of 20% of disease loci (*24*). Although these approaches give insight into the underlying mechanisms of the genetic signal and inform the design of targeted molecular experiments, they are often limited by the range and sample size of molecular data and disease-relevant tissues that are available, as well as by reproducibility (Fig. 2). The challenge now is to extend these efforts to less accessible disease-relevant cell types at different developmental stages and under different stimulatory and disease-relevant conditions to allow integration with large-scale genetic discovery efforts. The recently established Human Cell Atlas (HCA) is focused on providing greater resolution by generating reference maps of all human cells using both emerging single-cell "omics" and whole intact-tissue methodologies (*25*). Acceleration of progress in the development of approaches such as high-throughput screening and genetic manipulation coupled to cellular phenotyping is needed.

Access to certain human tissues remains a challenge, but the emergence of protocols for in vitro differentiation of human induced pluripotent stem cells (iPS), which can be differentiated into otherwise inaccessible cell types, offers the potential for disease-associated variants to be investigated in appropriate cell types. However, these studies are new and we are still learning much about how representative these systems will be for population-level medical applications.

Together, these efforts will accelerate translation of GWAS findings to therapeutic interventions through increased confidence in target identification.

Prediction, prevention, and prognosis

Common complex disease risk is conferred potentially by up to thousands of variants, prompting the development of polygenic risk scores to capture the likelihood of developing disease. As these variants are usually common in frequency with individually small contributions to overall risk, combining information from multiple variants, weighted by their effect size, has the potential to improve on the predictive value of clinical data alone. Genetic risk scores (GRSs) have been developed that comprise only signals that pass stringent criteria or that capture a greater proportion of genome-wide risk information (often termed polygenic risk scores). The choice of variants to include in the score is determined by the intended use of that score (e.g., to demonstrate the combined effect of specific genetic risk factors to overall

disease risk or the development of a predictive tool for clinical use) and their power is determined by the number of variants included in the score, the frequency of those variants in the population, the choice of weighting, and the contribution of environmental risk factors.

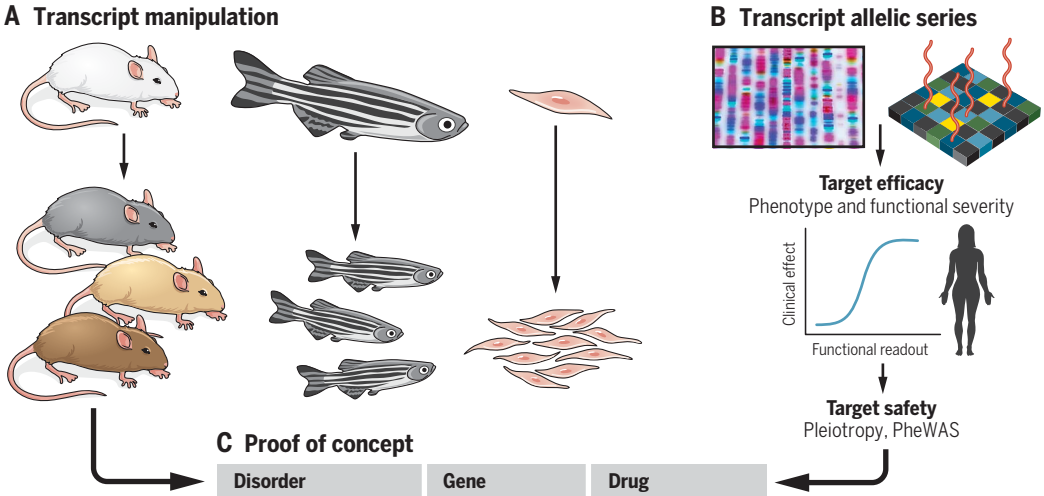
A recent study by Khera *et al*. (*26*) demonstrated the power of polygenic risk scores in the context of five common disease, showing that ~20% of the population had a polygenic threefold-increased risk of one or more common diseases; this was comparable to levels of risk conferred by rare disease-causing variants of high penetrance (*26*). A GRS for chronic obstructive pulmonary disease (COPD) demonstrated an almost fivefold relative risk when comparing high versus low genetic risk score deciles and when this was combined with absolute risk estimates for COPD among smokers, an absolute risk of COPD of 82.4% for smokers in the highest-risk score decile (compared with 17.4% for those in the lowest decile) (*27*). GRSs for obesity (*28*) and blood pressure (*29*), which are common risk factors for multiple diseases such as cardiovascular disease and type 2 diabetes and are considered to be modifiable, have also demonstrated substantial variation across the population. From a public health perspective, the extent to which these risk factors can be modified on a background of high genetic predisposition, and the most effective means of implementing such modifications, are research areas that should be prioritized to accelerate implementation.

The utility of GRSs in population-based genetic screening as a preventive strategy for complex diseases depends on the frequency of the disease being investigated as well as the genetic risk conferred by the associated variants. It is likely to be useful for highly prevalent complex conditions such as coronary artery disease, which affects between 10 and 20% of the population in Western countries (*30*). However, for some complex polygenic diseases with a low background prevalence (<5% of the population), even those at the highest genetic risk are more likely not to develop disease than to develop it: for example, in a disease with a population prevalence of 1% (such as rheumatoid arthritis), even those with a 20-fold increased risk will still have an 80% chance of not developing the condition on the basis of genetic risk alone. Additionally, as there are more individuals at lower genetic risk in the population, it has been shown that the majority of cases within the population will come from people at lower genetic risk for disease (*31*, *32*). Age-related macular degeneration is a case in point: it affects 5% of the >75-year-old population and was one of the first conditions in which GWAS identified genetic associations, with two genetic susceptibility variants conferring a 50-fold risk of disease development. However, only 20% of patients carry high-risk genetic variants, meaning that the majority of cases come from those with lower genetic risk, and genetic screening is not currently included in guidelines (*33*, *34*). Nonetheless, genetic information adds value over and above clinical characteristics in predicting the progression of macular degeneration, particularly in those with a less severe disease stage (*35*).

As such, implementation of GRSs for targeting of disease screening requires careful consideration in terms of which thresholds of risk are selected as the basis for screening decisions and the added value beyond clinical information alone (*36*). For common complex diseases such as stroke and coronary heart disease, where both genetic and environmental factors contribute to disease risk, environmental factors can have a greater influence (*37*, *38*). Modifiable environmental risk factors mean that identifying those at high genetic risk of developing disease can still have utility in effecting behavioral change. In a randomized control trial in asymptomatic first-degree relatives of patients with rheumatoid arthritis, disclosure of genetic risk information led to positive behavior modifications including increased smoking cessation and better dental hygiene, both of which are environmental risk factors (*39*). As GRS tests may call for lifestyle adaptations in response to risk of individual diseases, further research is required to evaluate how to implement best practices to facilitate such changes.

Beyond identifying those at highest risk of developing disease, GRSs can also inform the development of precision medicine approaches for earlier and more effective treatment by identifying those with the disease who are at highest risk of rapid progression or of more severe manifestations of disease (*26*, *40*). Furthermore, using disease-relevant quantitative traits to define the underlying biological processes characterizing the disease in an individual holds the promise of assisting with patient stratification; for example, patients with type 2 diabetes largely owing to insulin secretory defects may respond better to therapies focused on restoring insulin secretion as opposed to improving the action of insulin in target tissues (*40*). Such studies require large, prospective collections of patient samples with high-quality phenotype data to define disease trajectories and/or classify disease subtypes and will be essential if GRSs are to inform clinical care.

The implications for potential additional burden on clinical services of any genetic testing also requires consideration if advances are to translate to the clinical setting. For example, introducing genetic testing for variants that affect warfarin metabolism in routine clinical care of patients



Disorder	Gene	Drug
Type 2 Diabetes	*KCNJ11/ABCC8*	Sulphonylureas
Type 2 Diabetes	*PPARG*	Thiazolidinediones
Type 2 Diabetes	*SLC30A8*	ZnT8 antagonists
Osteoarthritis	*TGFB1*	INVOSSA
Hypocholesterolemia	*PCSK9*	PCSK9 inhibitors
Psoriasis	*IL23, IL23A*	Risankizumab

Fig. 2. Identifying therapeutic targets. (**A**) Effector transcripts identified at genetic signals are genetically manipulated to recapitulate in vivo effects on gene expression (e.g., CRIPSR knockdown or overexpression) in human cell lines (e.g., iPS cell–derived models) and in animal models, which can be phenotyped. (**B**) Additional alleles are identified using sequence data and assessed for their relationship to disease risk or related traits. To provide insight into the therapeutic window, in vitro functional severity and clinical severity are explored to establish the relationship between target perturbation and outcome. Potential adverse on-target effects are investigated using genome-wide datasets for other disorders [phenome-wide association studies (PheWAS)]. (**C**) Examples of therapeutic targets confirmed or identified by human GWAS.

receiving warfarin anticoagulation reported benefits (*41*). However, the 45 min required to obtain results affected the clinic workflow and potentially required a reorganization of service delivery (*41*).

GRSs have numerous potential applications in prediction and prevention, but care in their design and implementation is warranted, for example, with respect to transferability across and within populations (*42*). Most GRSs to date have been developed with data from European ancestry studies and although there is support for some generalizability of such scores across ancestries, it is evident that predictive power decreases with ancestral divergence and variation in minor allele frequencies as well as differences in relevant environmental exposures (*27*, *43*). If GRSs are to be incorporated into clinical decision-making or public health interventions, then the development of ancestry- and population-specific GRSs is vital to ensure equity in health care and optimal benefit to patients.

How can the discovery pipeline be accelerated?

Genomics in diverse populations

The majority of genetic association studies have focused on people of European ancestry. This not only leads to a bias in our understanding of genetic disease, but also results in a fundamental gap as different population characteristics can help identify and fine-map causal variants. At one end of the spectrum, isolated (founder) populations demonstrate high levels of genetic similarity (*44*), whereas African populations are characterized by high levels of genetic diversity (*45*). Thus, in isolated populations, protective or deleterious variants that are rare in the general population may be increased in frequency and thus be more easily detected. By contrast, the highly diverse African populations can help to determine the architecture of complex disease through fine-mapping and reveal associations that have been missed because of differences in allele frequency between populations (*45*). For example, a *G6PD* variant that is common (minor allele frequency, 11%) in African populations but rare or absent in European populations is associated with decreased HbA1c levels independently of blood glucose levels. Because raised HbA1c is a diagnostic marker for type 2 diabetes, a chronic condition that affects >400 million people globally, this could lead to substantial underdiagnosis of type 2 diabetes in African ancestry populations if based on HbA1c levels alone (*46*). Going forward, the next frontier in genomic medicine will require embracing whole-genome sequencing across all global populations to capture and understand the full spectrum of genetic variation and disease associations.

Deep phenotypic characterization

Retrospective and prospective longitudinal linkage to electronic health records (EHRs) in cohorts with genetic data can lead to better clinical characterization of the study population and enable discovery of new genetic associations with disease,

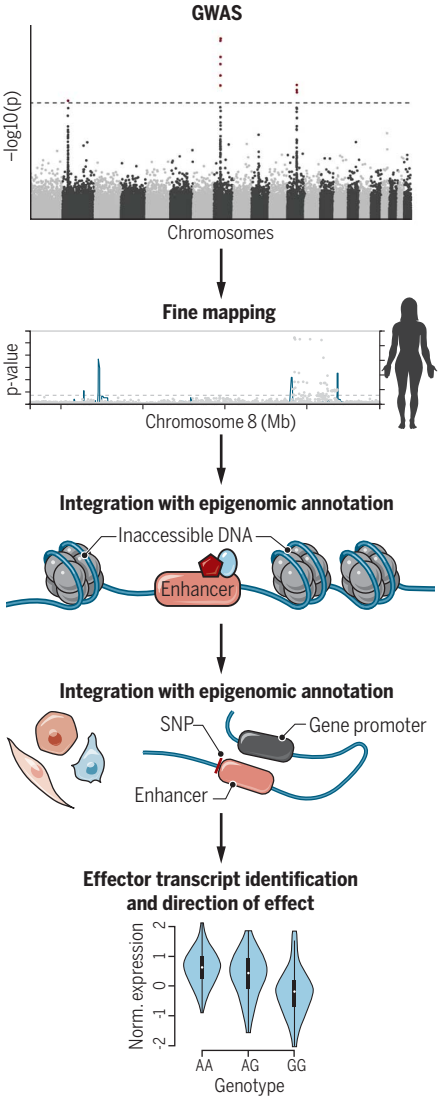


Fig. 3. Pathway to identifying causal variants. Trans-ethnic fine-mapping is used to refine genetic association signals and genomic annotation to prioritize likely causal variants. Variants in regulatory elements (e.g., enhancers) are mapped to the promoters and transcripts they regulate through conformation capture approaches (e.g., promoter Hi-C). Expression quantitative trait locus mapping can provide additional evidence for the effector transcripts and the direction of effect (e.g., increase or decrease in transcript levels).

disease subtypes, and disease-relevant quantitative phenotypes. Several large-scale biobanks and population-based cohorts, such as the UK Biobank (500,000 participants), the All of Us initiative (1,000,000+ participants), and the Million Veterans Programme, now include linkage to EHRs (*47*). There are already successful translational examples of coupling genomics to EHRs; for example, identification of loss-of-function mutations in *ANGPTL3* associated with the development of coronary artery disease and the subsequent development of an inactivating monoclonal antibody offering promise for disease prevention (*48*).

Unlike information and measurements collected in a research cohort setting, clinically derived EHRs have not been recorded with research in mind and are therefore even more prone to bias, inconsistency, and noise. Differences in how healthcare is delivered, for example, through a universal system [such as the National Health Service (NHS) in the United Kingdom] or through multiple independent providers (as in the United States), leads to differences in how the same condition might be recorded across countries, even when international coding systems are used. Particularly for fragmented health care systems, completeness of records is highly variable and this limits their utility to address many research questions, including those related to longitudinal measures. Even within a single system such as the NHS, regional differences in terms of coding exist and can vary from practice to practice and hospital to hospital, and detailed disease-specific records such as diagnostic scans are not yet fully captured by routine linkage in many healthcare systems. Furthermore, an understanding of the mechanisms that drive coding decisions is needed to identify potential sources of bias (e.g., the Quality and Outcomes Framework in the NHS whereby reward and incentivization of general practitioners influences coding practice). These variations exist not only across regions but also over time as coding systems, such as the World Health Organization International Classification of Disease, are updated.

Deeper phenotyping can also be achieved in research cohort settings through recall of participants. For example, imaging is being undertaken in 100,000 participants in UK Biobank, and imaging-derived traits can serve as markers of biological processes with a genetic underpinning and boost discovery in genetic association studies (*49*). Many cohorts now have consent to recall participants on the basis of either their phenotype (i.e., disease status) or genotype (e.g., carriers of a putative high-risk variant), thereby providing further opportunities to undertake deeper or more specific phenotypic characterization to address specific hypotheses. Recall-by-genotype studies are an exciting new tool when investigating causality in disease (*50*). The establishment of large-scale biobanks and registries geared toward genomics [as elegantly exemplified by the Nordic countries (*51*)] also means that previously difficult-to-reach genetic effects, such as gene-environment and gene-gene interactions [e.g., (*52*)], can be further explored.

The ability to refine phenotypes has clear benefits in our understanding of disease and disease endotypes, but the temptation to divide participants into smaller and smaller subgroups also runs the risk of reducing sample size, and consequently statistical power, for genetic discovery and so a balance must be struck. Furthermore, as phenotype definition becomes more nuanced and narrow, the potential for the variation in coding practices in EHR described above to affect interpretation becomes more pronounced.

Pragmatic definitions that capture the phenotype being studied with reasonable precision and minimal misclassification yet at the same time maximize sample size might be the optimal strategy for genetic association discovery where statistical power is a major consideration, in part because of the large multiple testing burden of genome-wide analyses.

Stricter phenotyping, such as that appropriate for descriptive classical epidemiological studies and clinical practice, could then be applied post hoc to delve deeper into the associations that are identified.

Genetic study designs that will be optimal to reap the rewards of deeper phenotyping will ideally require multidisciplinary collaboration that includes both genetic and classical epidemiology expertise as well as clinical insight. Researchers must be cognizant of subjective influences on phenotype definitions in large-scale EHR resources and take an integrative approach that also combines measures that might be less prone to bias (or at least, prone to different biases), such as biomarkers. The use of carefully considered sensitivity analyses to test the impact of assumptions made and misclassification will continue to be best practice in these studies.

Conclusion

A better understanding of the genetic etiology of complex diseases can provide new insights into fundamental biology and translational opportunities. In recognition of this translational potential, there is a rising number of high-profile, large-investment initiatives focused on genomics in medicine. These traverse public and private funding mechanisms to generate the large-scale clinical and biodata resources needed to spur innovation for personalized medicine and population health. This new, eagerly awaited digital health era is now becoming a tangible prospect. To ensure that the potential is realized, we recommend focusing on biological outcome measures where possible, accounting for nonadherence in studies of treatment response or ascertainment bias in prognostic studies, collecting prospectively recruited cohorts across diverse ancestries and with linkage to electronic health records so that population-specific PRS can be developed for a range of diseases, and, finally, investing time in determining how to implement genetic testing as a diagnostic test or to effect behavior change.

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