Leading Edge
Perspective

Cell

Genomic Medicine–Progress, Pitfalls, and Promise

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In the wake of the Human Genome Project (HGP), strong expectations were set for the timeline and impact of genomics on medicine—an anticipated transformation in the diagnosis, treatment, and prevention of disease. In this Perspective, we take stock of the nascent field of genomic medicine. In what areas, if any, is genomics delivering on this promise, or is the path to success clear? Where are we falling short, and why? What have been the unanticipated developments? Overall, we argue that the optimism surrounding the transformational potential of genomics on medicine remains justified, albeit with a considerably different form and timescale than originally projected. We also argue that the field needs to pivot back to basics, as understanding the entirety of the genotype-to-phenotype equation is a likely prerequisite for delivering on the full potential of the human genome to advance the human condition.

It is worth reminding ourselves that regardless of its impact on medicine, the sequencing of the human genome represents a monumental achievement. It is the blueprint that quite literally specifies how to build a human, even if we do not yet fully understand the means by which it does so. To have gone from observing the double helix to the assembly and rudimentary understanding of the human genome's 3 billion nucleotides in 50 years is a stunning trajectory, with no obvious equivalent other than our progression from the first powered flight to a moon landing in about the same amount of time. Furthermore, although it has only been 15 years since an achievement that will be remembered for millennia, the Human Genome Project (HGP) has already had scientific and economic impacts that more than amply justify its cost (National Human Genome Research Institute, 2013).

This praise notwithstanding, we should not forget that the prioritization and cost of the HGP were justified by, and its completion celebrated with, the setting of ambitious expectations about the time frame on which it would transform the diagnosis, treatment, and prevention of a broad swath of human diseases. In this Perspective, we attempt to take stock of the progress made, as well as the hurdles to, the clinical translation of the human genome—the nascent field of genomic medicine. For the citizens that funded it, has the bet of the HGP paid off? If it has not, will it ever? Is the value proposition as originally laid out still justified, or do we need to recalibrate?

This is a large topic to undertake, and we have organized this review as follows. First, we summarize the key technological developments since the HGP. Second, we consider the successes and challenges to genomic medicine in four areas: common inherited diseases, rare inherited diseases, reproductive health, and cancer (Figures 1 and 2). Finally, we take stock of the field as a whole and suggest areas that warrant further investment to fully unlock its potential.

Beyond the HGP: From One to Millions of Human Genomes

The HGP was completed in 2003 at an estimated cost of $2.7 billion, primarily through the brute-force scaling of automated Sanger sequencing of large insert clones, followed by hierarchical assembly (International Human Genome Sequencing Consortium, 2004). The commonplace use of the article "the" in conjunction with "human genome" emphasizes the nearly perfect similarity of individual humans to one another (~99.9%) but downplays the millions of differences (~0.1%) that make each of us genetically unique. However, the *raison d'etre* for the field of human genetics lies not with our similarities but our differences—more specifically, with disentangling how our genotypic differences underlie our phenotypic differences.

If there is one area where we have over-delivered as a field since the HGP, it is in the development and deployment of technologies for ascertaining interindividual genetic differences. Two technologies now critically underpin nearly every aspect of genomic medicine. First, high-density DNA microarrays can be used to genotype millions of specific positions in each of many human genomes. Coupled with population-based maps of linkage disequilibrium (LD), array-based genotyping enables the ascertainment of most common genetic variation in a human genome for a remarkably low cost (initially hundreds, now tens, of dollars per individual) (Gunderson et al., 2005). Second, massively parallel DNA sequencing technologies, which have steadily improved since their introduction in 2005, can generate billions of short sequencing reads within a day or less (Shendure et al., 2017). Also known as next-generation sequencing (NGS),

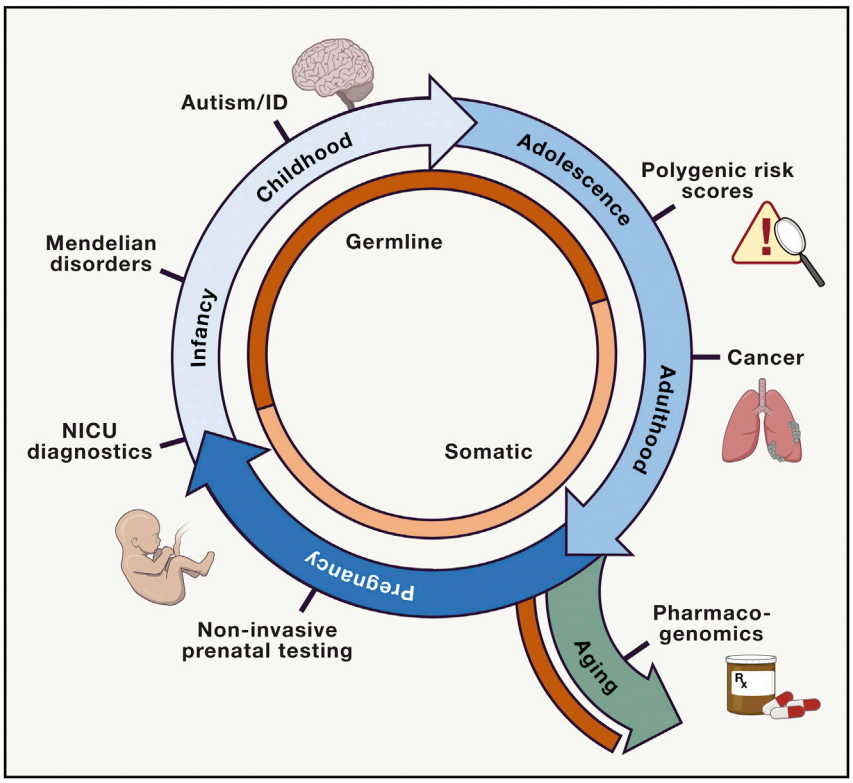

Figure 1. Genomic Medicine throughout the Human Life Cycle

There are many modalities for genomics to have an impact on clinical care, with entry points for application that span the human life cycle from conception to death.

such platforms now permit the near-comprehensive ascertainment of both rare and common genetic variation for about $1,000 per individual (or a few hundred dollars, if one selectively sequences the exome or coding regions of the genome). Importantly, both array-based genotyping and NGS depend heavily on the availability of a high-quality reference genome such as the one generated by the HGP, the former for designing probes with which to query positions of common variation and the latter for mapping short reads to, so as to localize *bona fide* variants and distinguish them from sequencing errors. Of note, NGS has also become an incredibly powerful tool for quantifying a broad range of molecular phenomena, e.g., transcriptomes (RNA sequencing, RNA-seq), protein-DNA binding (chromatin immunoprecipitation sequencing, ChIP-seq), etc., essentially through the counting of molecules (Shendure and Lieberman Aiden, 2012).

The precipitous rate at which genotyping and sequencing costs have dropped was scarcely anticipated at the completion of the HGP in 2003. Given that it has only been a few years since the full maturation of these technologies, the number of humans that have been already been genotyped by arrays or subjected to exome or genome sequencing is staggering. Although a comprehensive count is not easily achieved, it is estimated that the number of individuals genotyped by direct-to-consumer genealogy companies was less than 1 million as recently as 2014 but 3 million by 2016 and 12 million by 2018 (Figure 3, left). The number of individual humans whose genomes have been sequenced is estimated to have gone from 1 in 2003 to over 50,000 by 2015 and over 1.5 million by 2018 (Figure 3, right).

These trends are driven by distinct forces in the research, medical, and direct-to-consumer fields and do not show any signs of abating. For example, large cohorts, including nationwide efforts such as the UK Biobank and US All of Us programs, are collectively targeting the genome sequencing of over 25 million humans (Global Genomic Medicine Collaborative, 2018).

Genomic Medicine → Common Disease

Whether fairly or not, much of the discussion about the perceived shortcomings of genomic medicine has centered on genome-wide association studies (GWASs). In brief, most genetic variants in individual human genomes are common (allele frequency > 1%), leading to the hypothesis that our individual genetic risk for common diseases derives mostly from common variants, as opposed to the rare variants or *de novo* mutations that underlie Mendelian disorders (Manolio et al., 2009). The GWAS framework, first proposed by Risch and Merikangas in 1996 as an alternative to linkage studies (which had succeeded for Mendelian diseases but largely failed for common diseases), is designed to detect even subtle associations between common variants and common diseases on a systematic, genome-wide basis (Risch and Merikangas, 1996). Around 2005, several developments converged to enable well-powered GWAS, including public catalogs of common human genetic variants, initial maps of LD among common variants in human populations, and cost-effective array-based genotyping technologies (Collins et al., 1997; Gunderson et al., 2005; International HapMap Consortium, 2005). Over the ensuing decade, through the genome-wide genotyping of increasingly large cohorts of cases and controls, the imputation of additional genotypes based on LD maps, and the application of appropriately corrected statistical tests, the field has collectively discovered over 100,000 unique, robust associations between common variants and common diseases (Burdett et al., 2018).

This sounds like success—why are we so unhappy? It is worth taking a step back and asking: for what reasons do we want to investigate the genetic basis for common human diseases in the first place? One motivation is risk prediction—that is, using genetic factors to better stratify which individuals are at higher risk for specific common diseases, which may facilitate preventative measures and/or the better allocation of resources across a heterogeneously susceptible population. A second motivation

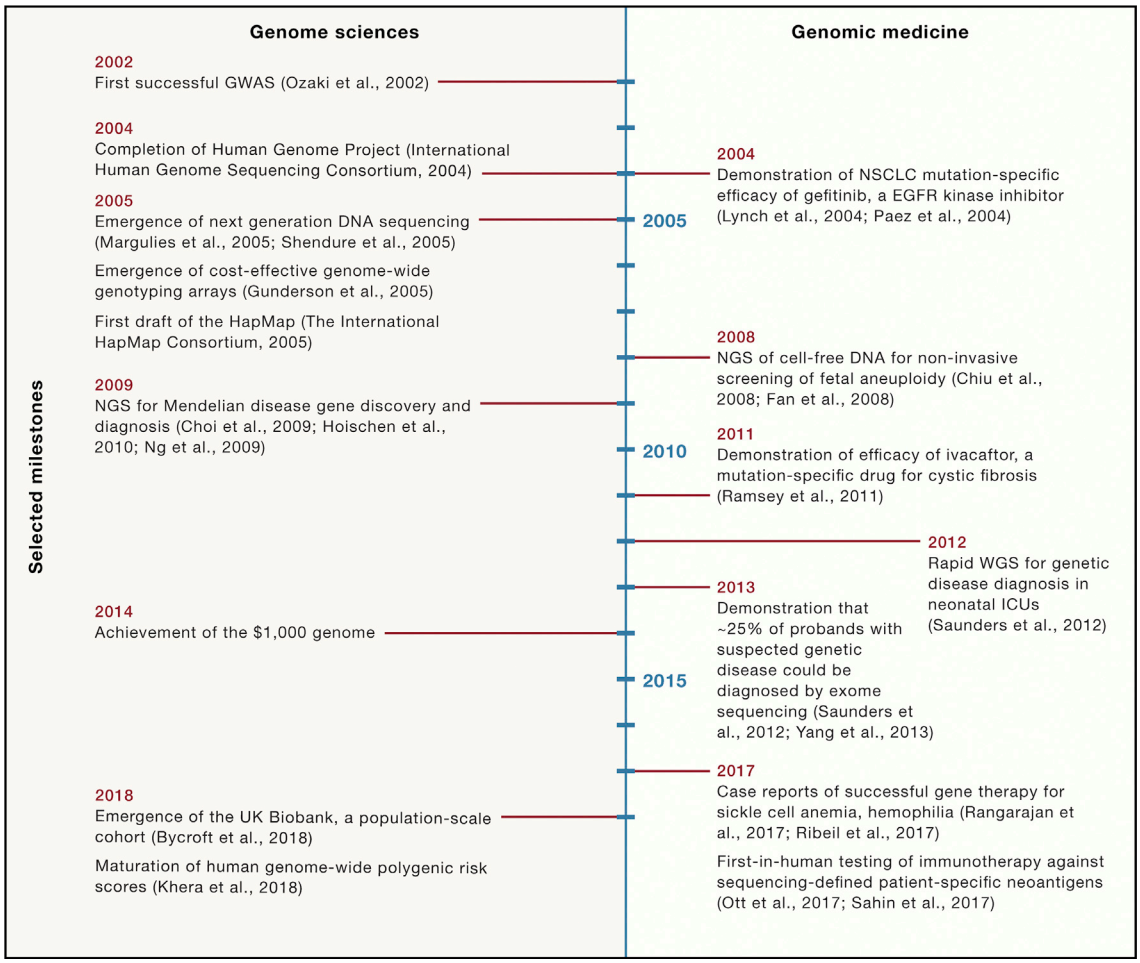

Figure 2. Past Milestones for Genome Sciences and Genomic Medicine
A timeline on selected milestones in the progression of the genome sciences (left) and genomic medicine (right).

is target identification, grounded in the view that our historical approach to understanding the pathogenesis of common diseases has been largely *ad hoc* and therefore prone to false positives and negatives. In contrast, GWASs provide a systematic, genome-wide approach for identifying genes that play a role in each disease. As this should result in a longer, higher-quality list of potential drug targets, GWASs were/are expected by some to accelerate our ability to develop effective therapies.

So what has gone wrong? A first challenge, primarily to the goal of risk prediction, has been that with few exceptions, the genetic component of common human disease risk consists of an extremely large number of variants of small effects, the vast majority of which would require astronomically large study sizes to definitively implicate. A subset of these weakly associated variants achieves genome-wide significance, but the effect sizes are usually modest even for these, and they have limited predictive power whether taken individually or considered together.

A second challenge is that for most common diseases, genome-wide-significant common variants turn out to explain only a small minority of their heritability. This was recognized relatively early in the GWAS era, and many potential explanations were put forth (Manolio et al., 2009). A leading hypothesis that emerged was that rare variants might explain a substantial fraction of this "missing heritability," motivating large-scale exome- and genome-sequencing studies of common diseases. However, even when reasonably well-powered studies are conducted, this hypothesis has not borne out, or at least not yet. For example, in type II diabetes, it was shown that lower-frequency variants are collectively likely to contribute less to heritability than common variants (Fuchsberger et al., 2016). Recently, the mystery of missing heritability has been solved to a large extent by the demonstration that common variants *as a class* account for a much larger proportion of heritability than the subset that achieve genome-wide significance (Yang et al., 2010).

A third challenge, primarily to the goal of therapeutic target identification, has been that the same LD structure that makes GWAS considerably cheaper to execute ironically limits its resolution, the consequence being that we have succeeded in implicating tens of thousands of haplotypes rather than tens of thousands of specific variants. Although considerable effort has been invested in fine-mapping, the task of confidently dissecting which variants are causally responsible for each

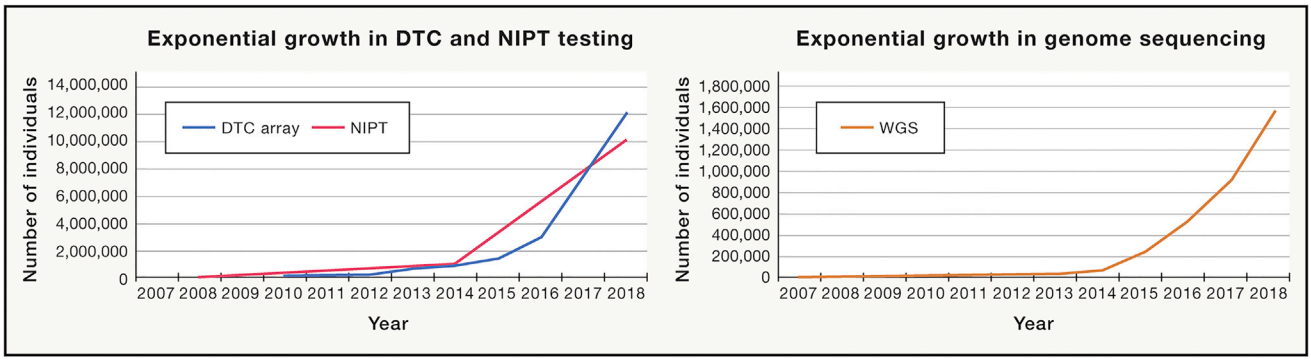

Figure 3. Exponential Growth in Genomic Testing

We show estimates of number of individuals that have been received genetic testing in the form of direct-to-consumer microarrays (DTC) and non-invasive prenatal testing (NIPT) (left) and whole-genome sequencing (WGS) (right) as a function of time. For NIPT, estimates are from Chiu et al. (2008), Fan et al. (2008), Liu et al. (2018), and Yuzuki (2015). For DTC and WGS, estimates are from Illumina (personal communication), with estimates of WGS based on equivalents of 30X coverage.

observed association between a haplotype and a common disease can be maddening.

A fourth challenge, also more relevant to the goal of target identification, is that the vast majority of the GWAS-defined heritability signal partitions to non-coding regions of the genome, and much of it to cell-type-specific regulatory elements (Finucane et al., 2015). As most enhancers are not definitively linked to genes, even if one is successful in pinpointing a causal regulatory variant, identifying the gene through which it mediates its subtle effects on disease risk, not to mention the mechanisms by which the gene acts, represents additional hurdles. A major rate limiter to further progress in this field is that we lack scalable solutions for any of these tasks, in part because they require non-trivial experiments incorporating disease-specific biology.

A fifth challenge, raised in a recent perspective by Boyle & Pritchard, is that gene regulatory networks are so densely interconnected, and GWAS so well-powered to detect subtle effects, that many *bona fide* associations may be due to genes that subtly impact genes in core pathways but themselves are only peripherally relevant to the phenotype (Boyle et al., 2017). An implication of this "omnigenic" model is that many if not the vast majority of GWAS signals, even if successfully fine-mapped, may not meaningfully inform target identification nor our understanding of disease.

Finally, as the cohorts required to identify additional GWAS signals grow larger and larger, a broader question is when do we stop caring? How can one credibly argue for the marginal value of the 100th significant association with type II diabetes, when the vast majority of the first 99 have larger effect sizes but have yet to be effectively followed up on with respect to identifying the causal variants and genes?

On one hand, we feel that these are fair concerns to raise, provided that they are raised constructively. At the same time, for a goal as audacious as dissecting the basis of all common human diseases, we should not expect that the solution to every obstacle should have been established in advance, or we would have never gotten started. Furthermore, despite these non-trivial challenges, we actually remain quite positive with regard to the ultimate impact that GWASs will have on the diagnosis, treatment, and prevention of common diseases. There are four main reasons for our optimism.

First, it is retrospectively unsurprising that many of the strongest GWAS associations came early, as smaller studies were only powered to detect large effects, and large effects seem more likely to be mediated through core genes and pathways. The vast majority of GWASs have been conducted in European populations (Visscher et al., 2017), and with the exception of some unique subpopulations, we are skeptical of the marginal value of ever-larger studies in these same populations for the purpose of gene discovery. However, each non-European population represents a fresh source of variants common to that population, and comparatively smaller studies in these populations may yield additional large-effect signals (presumably easier to fine-map and more likely to be therapeutically relevant) for a reasonable cost. Furthermore, smaller studies in populations with less LD (e.g., African ancestry) can facilitate the fine-mapping of associations identified in other populations (Willer et al., 2013).

Second, there are an increasing number of clear examples of GWASs shedding light on the specific pathways and cell types that are most relevant for particular common diseases, of association signals being followed up on to implicate specific variants and genes, and of these insights having meaningful consequences for how the disease will be approached from a drug-discovery perspective. These are reviewed elsewhere (Visscher et al., 2017), but a particularly compelling example is the use of GWAS together with Mendelian randomization to convincingly demonstrate that the associations of LDL cholesterol and triglyceride levels with coronary artery disease (CAD) reflect causal relationships, whereas the association of HDL cholesterol levels with CAD does not (Do et al., 2013; Voight et al., 2012). A more general observation is that the pharmaceutical industry is an increasingly sophisticated consumer of GWAS analyses in order to make maximally well-informed decisions about target selection for drug discovery (Nelson et al., 2015). On a related topic, the list of genetic variants that impact drug response, i.e., pharmacogenomic interactions, is growing, with many of the newer discoveries made via GWASs (Motsinger-Reif et al.,

2013). Of note, despite their clear clinical utility and often large effect sizes, pharmacogenomics has been slow to achieve clinical adoption, illustrating how the science is often only the first of many challenges.

Third, although we are still far from where we need to be, the toolkit for identifying the variants and genes that causally underlie GWAS signals is steadily improving. These include statistical methods that incorporate biochemical annotations (to identify which variants lie in *bona fide* regulatory regions), expression quantitative trait locus (QTL) studies (to locate genes whose expression is modulated by the same haplotype as a disease), massively parallel reporter assays (to pinpoint variants with regulatory effects), and CRISPR/Cas9 genome editing (to test the functional consequences of a specific variant, or potentially libraries of variants, in their endogenous genomic context). Methods are also advancing for linking regulatory elements to the gene(s) that they regulate, e.g., by 3C-based identification of ''loops'' or by coupling CRISPR/Cas9 perturbations and single-cell readouts (Gasperini et al., 2019; Mumbach et al., 2016). To date, such tools have been applied to investigate only a small number of GWAS signals. However, as they become more widely used and more scalable, the number of common disease associations for which the causal variants and genes are known is likely to grow.

Fourth, as long evidenced by plant and animal breeding programs, we need not restrict ourselves to genome-wide significant associations to build phenotypic predictors from GWAS results. Polygenic risk scores (PRSs) are not a new concept (Wray et al., 2013), but an increasing number of studies are showing that PRSs that incorporate information from common variants throughout the genome (including from vast numbers of single nucleotide variants [SNVs] that fail to achieve genome-wide significance) achieve reasonable performance in stratifying risk for complex diseases in humans. For example, Khera et al. recently reported that a PRS trained on a portion of the UK Biobank (training set) identifies 2.5% of the remaining participants (test set) that are at 4-fold higher risk for CAD, essentially equivalent to monogenic hypercholesterolemia but impacting a much larger proportion of the population (Khera et al., 2018). Analogous results were obtained for breast cancer and obesity. Through PRS, we may more effectively deliver on the HGP's promise of better predicting individual risk for common diseases, without necessarily requiring any understanding of the biology on which those predictors are based.

In summary, with respect to the genetic study of common diseases, the glass is both half empty and half full. We are not saying that there is not more to be learned from additional GWASs, but in a world of finite resources, we should be skeptical of the commitment to ever-larger GWASs of specific diseases when we are already drowning in robust associations that remain incompletely followed up on. It is clear that following up *bona fide* associations can provide insights, both for biology and drug discovery. Shifting resources toward developing and implementing the necessary computational and experimental tools for pinpointing the specific variants, genes, and mechanisms that underlie established association signals should be prioritized, in hopes of finishing our incomplete sentences at a faster rate than we are starting new ones. A qualification is that the developments around PRSs, which are potentially clinically useful without requiring fine-mapping or biological understanding, are exciting and warrant further exploration. It is notable that the training and validation of PRSs for a broad range of human traits and diseases has been strongly enabled by the effectively unrestricted availability of a massive, population-scale cohort, the UK Biobank (Bycroft et al., 2018). Such cohorts, and their amalgamation, likely represent the future of common disease genetics, as opposed to disease-specific cohorts.

Genomic Medicine → Rare Disease

An area in which the glass is clearly much fuller is that of rare disease. It is estimated that there are ~7,000 Mendelian or monogenic disorders that collectively impact ~0.4% of live births (~8% if congenital anomalies are included) but account for a much larger proportion of morbidity and mortality (e.g., by one study, 71% of pediatric hospital admissions) (Baird et al., 1988; Chong et al., 2015; McCandless et al., 2004). To better serve these patients as well as to advance knowledge, a defining quest for human genetics has been to comprehensively delineate the genetic basis of Mendelian disorders. In the era prior to the HGP, linkage mapping followed by arduous molecular cloning was used to ''solve'' over 1,000 Mendelian disorders. The reference human genome greatly accelerated the latter task, enabling a steady rate of discovery throughout the 2000s. Since 2009, exome or genome sequencing, facilitated by NGS, the reference human genome, and catalogs of common genetic variation, have driven a renaissance in this field (Choi et al., 2009; Hoischen et al., 2010; Ng et al., 2009). These approaches have been particularly useful for diseases whose inheritance patterns are not amenable to linkage analysis, e.g., those predominantly caused by *de novo* dominant mutations or somatic mosaicism, resolvable by ''trio-based sequencing'' of unaffected parents and an affected offspring.

One of the larger surprises of this renaissance has been the substantial proportion of cases of neurodevelopmental disorders—in particular, diagnoses of intellectual disability (ID) and/or autism spectrum disorder (ASD)—that are attributable to *de novo* mutations. For example, it was recently estimated that *de novo* events including point mutations and copy-number variants (CNVs) account for at least 30% and possibly as much as 60% of simplex ASD (Iossifov et al., 2014). Although the waters muddy considerably for patients in whom causal mutations cannot yet be identified, both Mendelian disease and neurodevelopmental disorders are broadly considered to be areas of solid and ongoing success, at least with respect to elucidating the underlying genetic factors.

For Mendelian and neurodevelopmental disorders, NGS, coupled with the reference human genome, are transforming not only gene discovery but also how clinical diagnoses are made. Particularly given that the diagnosis of many or most Mendelian disorders based on clinical features alone remains challenging, directly sequencing a patient's and/or family's exome(s) can provide a definitive answer and circumvent so-called diagnostic odysseys. A landmark study in 2013 showed that ~25% of probands with potentially genetic conditions could be diagnosed by exome sequencing, a proportion that will only rise as our understanding of monogenic disease becomes

more comprehensive (Yang et al., 2013). A more recent study from the same group showed that over one-third of cases that were unsolved by a standardized pipeline could be resolved by focused investigation (Eldomery et al., 2017).

A recurrent criticism is that diagnoses are not terribly useful when ''cures'' are not available, as is the case for the vast majority of Mendelian diseases. This is misguided, as accurate diagnoses can provide meaningful resolution for patients and families, connect them to disease-specific support networks, inform prognosis and co-morbidities, and facilitate family planning. For ID and ASD as well, ''molecular stratification,'' i.e., the identification of what specific gene underlies a particular patient's condition, is useful for exactly the same reasons (Bernier et al., 2014).

Particularly given the contribution of Mendelian disorders to infant mortality in developed countries (by one study, 23% of infant deaths), the pioneering efforts of Kingsmore and colleagues toward sub-24 h diagnoses of rare genetic conditions in neonatal intensive care unit (NICU) patients warrants mention. Studies from multiple groups have shown that rapid whole-genome sequencing can result in diagnoses for as many as half of acutely ill inpatient infants, informing clinical management as well as reducing inpatient costs in about half those cases. Given the stakes, we would be unsurprised to see this further develop into the standard of care in the near future (Farnaes et al., 2018; Meng et al., 2017; Saunders et al., 2012; Willig et al., 2015).

A noteworthy set of genes are the 59 designated by the American College of Medical Genetics (ACMG) to be sufficiently ''medically actionable'' so as to merit reporting as secondary findings in the context of clinical genetic testing done for other purposes (Kalia et al., 2017). The paradigmatic examples from the ACMG 59 are *BRCA1* and *BRCA2*, wherein pathogenic mutations are associated with early-onset breast and ovarian cancers, the risk for which can be mitigated by appropriate interventions (e.g., mastectomy, oophorectomy). Other examples include *BMPR1A* and *SMAD4*, wherein pathogenic mutations are associated with polyps and ultimately colon cancer, morbidity from which can be mitigated by frequent screening. Genes like *BRCA1* and *BRCA2* have already been sequenced in millions of individuals; most other genes on this list are far behind but are increasingly included on gene panels and naturally ascertained through exome or genome sequencing. Although the development of guidelines for reporting and actionability around these genes is an unquestionably positive development, at least two major challenges remain.

A first challenge is that of variant interpretation. A key distinction between secondary findings in ACMG 59 genes versus conventional findings in Mendelian disorders is that with the former, the patient has not yet developed the phenotype, such that the prior probability that a rare variant or *de novo* mutation is pathogenic is much lower. Although nonsense mutations are generally interpretable as pathogenic, missense and other mutations in these genes are typically classified as variants of unknown significance (VUS), a label that is confusing for physicians and anxiety-provoking for patients. Particularly as sequencing is extended to ever-larger populations, and as more genes become medically actionable, the number of VUS will exponentially grow (Starita et al., 2017). The problem is mitigated by public data sharing, but by no means solved, as the vast majority of rare variants may occur in only a handful of living humans, insufficient for the definitive assignment of risk. Toward solving this, we and others are pursuing scalable approaches for experimentally testing the functional consequences of variants, the vast majority of which have yet to be observed in a patient, via *in vitro* assays that capture the gene's disease-relevant function (Starita et al., 2017). As one example, for *BRCA1*, we and colleagues recently used saturation genome editing to experimentally test >96% of all possible SNVs in the gene's RING and BRCT domains, with results that strongly correlate with available clinical interpretations (Findlay et al., 2018).

A second challenge is that of penetrance, i.e., the proportion of individuals with a mutation in a gene that will actually express the associated phenotype. Historically, we have estimated the penetrance of mutations in genes such as *BRCA1* and *BRCA2* by studying patients and their families. However, these families may be enriched for modifiers in a way that results in penetrance being overestimated. Through cohorts such as the UK Biobank and All of Us, sufficiently powered studies on unselected populations are increasingly realistic, potentially allowing for a correction of penetrance estimates for genes such as *BRCA1* and *BRCA2* and the first such estimates for rare diseases for which they have heretofore not been possible. On a related point, it seems that we will increasingly be in a position to identify and exploit modifiers of penetrance for disorders caused by rare variants. There is accumulating evidence that common genetic variants, in aggregate, are formidable modifiers of penetrance and expressivity. For example, *BRCA1* mutation carriers can be stratified into those at high versus low risk for breast or ovarian cancer on the basis of common variants (Couch et al., 2013). Common genetic variants also appear to contribute substantially to risk for neurodevelopmental disorders including autism (Niemi et al., 2018; Weiner et al., 2017). These findings suggest that the PRS approach highlighted above will be relevant for not only common diseases but also Mendelian and neurodevelopmental disorders.

In the past few years, with increasing investment from pharma in rare diseases (Litterman et al., 2014), the second coming of gene therapy (Dunbar et al., 2018), and the third wave of genome editing platforms (Gaj et al., 2013), there is justified excitement about the development of therapies, and possibly even cures, for select Mendelian disorders. A full consideration of these is beyond the scope of this Perspective, but we briefly highlight four examples. (1) Cystic fibrosis: In 2011, over 2 decades after the gene underlying cystic fibrosis (CF) was mapped, a new drug, ivacaftor, was demonstrated to be efficacious in improving lung function for CF patients bearing a mutation for which the drug was designed (Ramsey et al., 2011). Compounds directed at modulating the activity of other CFTR alleles, e.g., lumacaftor for the common delta-F508 mutation, are actively being developed. (2) Sickle cell anemia: A recent single-patient report described effective, sustained remission of sickle cell anemia subsequent to lentiviral transfer of an antisickling beta-globin variant (Ribeil et al., 2017). (3) Hemophilia: A recent phase 1-2 trial in patients with severe hemophilia A showed that a single dose of an adeno-associated virus (AAV) vector bearing human *F8* consistently resulted in stable levels of factor VIII, reduced

bleeding, few adverse events, and no neutralizing antibodies (Rangarajan et al., 2017). (4) Muscular dystrophy: Although still unpublished, early results from three patients with Duchenne muscular dystrophy, treated by AAV delivery of a shortened form of dystrophin, included surprisingly high dystrophin levels, reduced creatine kinase, and anecdotes of massive clinical improvement (Herper, 2018). These and other recent reports, together with major recent investments in the clinical translation of genome editing, suggest that we are in for an exciting few years in this space. Although Mendelian diseases are rare, and it will likely only be a small subset for which effective treatments will be developed in the near future, their impact on young patients and their families can be profound and should not be discounted. These developments also illustrate the decades-long road, but one that can ultimately prove very worthwhile, between the basic science of mapping disease genes and the translational science of developing effective therapies.

The study of rare diseases can also have major implications for common diseases, including for guiding therapeutic strategies. The classic example is familial hypercholesterolemia, an autosomal dominant condition whose mapping to the LDL receptor helped make the case for statins, now used by millions of individuals for primary prevention of atherosclerotic cardiovascular disease (Stossel, 2008). A more recent example is *PCSK9*, wherein loss-of-function (LOF) mutations are associated with lower cholesterol, motivating the development of agents to inhibit its protein product, several of which were recently shown to be effective in lowering LDL cholesterol levels more effectively than statins (Chaudhary et al., 2017).

Motivated by these and other successes, there are now several efforts to systematically discover instances in which LOF mutations in living humans might inform drug development. For example, through ''hypothesis-free'' exome sequencing of a cohort of ~50,000 individuals for which healthcare records were available, Dewey and colleagues discovered that heterozygous LOF mutations in *ANGPTL3* were associated with lower cholesterol levels. Correspondingly, a monoclonal antibody against this same gene lowered cholesterol in animal models and healthy human volunteers (Chaudhary et al., 2017; Dewey et al., 2017).

Whereas heterozygous LOF carriers for nearly any haplosufficient gene can be found in such large cohorts, there are also efforts underway to leverage high levels of consanguinity in some populations to identify and deeply phenotype humans bearing homozygous LOF mutations for as many genes as possible (Perdigoto, 2017). As an unconventional example of how insights from such homozygous LOF patients can inform even common infectious diseases, consider *CCR5*, a gene for which LOF results in resistance to HIV acquisition. A brilliant study showed that a stem cell transplant from a donor with homozygous LOF of *CCR5* to a patient with HIV resulted in long-term control of viral load without antiretroviral therapy (Hütter et al., 2009). An obvious next step to explore is whether gene editing of *CCR5* in autologous cells is an effective strategy for long-term control of HIV (Tebas et al., 2014), i.e., as a potential alternative to lifelong antiretroviral treatment.

Most of the threads on the road between rare disease genetics and effective therapies for rare and common diseases are still works in progress. However, there is now ample reason, much more so than even 2 years ago, to believe that a reasonable fraction of them will succeed.

Genomic Medicine → Prenatal and Reproductive Health

Nowhere has the impact of genomic medicine on clinical practice been stronger than in prenatal and reproductive diagnostics. A sea change has already occurred in non-invasive screening for fetal trisomies (i.e., non-invasive prenatal testing, NIPT), both in terms of the screening methodologies themselves and in the risk categories of the pregnancies being tested. Assisted reproductive technology is offering prospective parents increasing quantities of genetic information on fertilized embryos before implantation. However, the information provided can sometimes complicate, rather than clarify, clinical decision-making. In this section, we briefly summarize the technologies underlying these tests, the types of information they provide to clinicians and patients, and the implications—clinical and ethical—of their continued growth.

Following its discovery in 1948 (Mandel and Metais, 1948), plasma-borne DNA remained essentially a curiosity until the discovery that the variable tissue sources of these fragments provide a window into malignancy and pregnancy (Leon et al., 1977; Lo et al., 1997; Stroun et al., 1987). While non-invasive screening for fetal abnormalities is not new, the accuracy and resolution of cell-free DNA (cfDNA)-based genetic tests for trisomies led to their emergence as the fastest adopted molecular test in the history of medicine and arguably the largest success story of genomic medicine to date. NIPT directed at identifying common fetal aneuploidies include ''chromosomal counting'' methods based on low-pass whole-genome sequencing (Chiu et al., 2008; Fan et al., 2008), targeted sequencing derivatives that potentially reduce the likelihood of incidental findings (Sparks et al., 2012; Zimmermann et al., 2012), and purely microarray-based assays (Juneau et al., 2014). The performance of tests implementing each of these approaches has been consistently strong in both high- and low-risk cohorts (Bianchi et al., 2014; Dar et al., 2016; Norton and Wapner, 2015), which has, together with the comparatively poor performance of contemporary alternatives, no doubt accelerated their widespread and rapid adoption.

The resolution of NIPT continues to improve, enabling clinicians to evaluate the risk of additional classes of genetic lesions beyond chromosomal aneuploidy. Recently, cfDNA-based tests able to detect sub-chromosomal abnormalities, such as microdeletions implicated in Prader-Willi or Angelman syndromes, were described and added to some existing commercial NIPT offerings (Srinivasan et al., 2013; Wapner et al., 2015). These tests mirror the growth in non-invasive testing for single-gene disorders, wherein the detection of specific risk alleles is obtained through more targeted means (Camunas-Soler et al., 2018). In proof-of-concept studies, we and others have shown that the whole-genome sequence of a fetus can be ascertained with samples obtained non-invasively from the parents (Chan et al., 2016; Fan et al., 2012; Kitzman et al., 2012). For prospective parents with difficulties with conception or with known risk of recessive disease, preimplantation genetic diagnosis (PGD) offers the *in vitro* fertilization and profiling of multiple embryos

prior to implantation. Mirroring the advances in NIPT, the resolution of PGD has increased in recent years, such that determination of the whole genome of each embryo is now possible (Hou et al., 2013; Kumar et al., 2015).

Looking forward, it seems plausible to suggest that the future of reproductive genetics may be a single, comprehensive test that simultaneously interrogates a pregnancy or fertilized zygote for aneuploidy, structural variants, and inherited variants or *de novo* mutations potentially causing any one of the >3,000 Mendelian disorders with known causes. While such whole-genome tests are technically within reach, multiple challenges remain to their widespread adoption. First and foremost is the challenge of interpretation of exhaustive test results: given the inevitably large number of VUSs as well as the challenges in quantifying penetrance discussed above, how much information is too much for a clinician, a genetic counselor, or a prospective parent? Second, substantial technical and logistical obstacles—including experimental complexity, scalability, necessary expertise, and cost—remain significant impediments to clinical adoption. Finally, the ethical considerations surrounding prenatal testing, which are not unique to cfDNA-based NIPT, are magnified in light of increasing resolution as well as the development of PRS, with potential for prenatal prediction of adult-onset diseases as well as non-disease traits. Greater scrutiny and regulatory oversight of the reproductive genetics industry is sorely needed.

Genomic Medicine → Cancer

The public's perception of the successes and struggles of genomic medicine has largely focused on cancer, which competes with heart disease for status as the leading cause of death in developed countries. Here, we consider cancer separately from other common diseases, because although there are inherited factors that can modulate risk (e.g., common variants, *BRCA1* mutations, etc.), it is ultimately a disease of somatic mutation. With NGS and projects such as The Cancer Genome Atlas (TCGA), the past decade has witnessed enormous strides toward comprehensively cataloging the genes and mutations that can serve as drivers of oncogenesis, essentially by exome or genome sequencing of thousands of tumor-normal matched sample pairs. A recent pan-cancer analysis across the entire TCGA dataset identified a consensus list of 299 driver genes of common cancers (Bailey et al., 2018). Furthermore, we have not yet saturated discovery of such drivers, potentially motivating a much larger version of the TCGA (Lawrence et al., 2014). However, given finite resources and analogous to GWASs, one wonders about the marginal value of the 300th driver gene, which is likely mutated in only a very small fraction of cancers, particularly when the first 299 remain understudied and therapeutically underexploited. Nonetheless, the catalog achieved to date is a wonderful accomplishment, a necessary prelude to a rational attack on the so-called emperor of maladies.

Far more so than in the other areas discussed above, driver genes and mutations in cancer provide clear molecular targets for therapeutic agents. The paradigmatic example is that non-small cell lung cancers with activating somatic mutations in the EGFR kinase, but not those without, are effectively treated with the EGFR kinase inhibitor gefitinib (Paez et al., 2004). Taking the TCGA as a reasonably representative broad survey, about half of common tumors contain one or more clinically relevant mutations, predicting sensitivity or resistance to specific agents or suggesting clinical trial eligibility (Bailey et al., 2018). But how efficacious are such "precision therapies"? On the one hand, there are accumulating anecdotes of patients who have had remarkable responses, including complete remissions, to agents whose selection was guided by genomic information. On the other hand, to the extent that it has been systematically studied, treating patients with therapies that are molecularly matched to their tumors more typically extends progression-free survival by weeks or months, rather than years (Radovich et al., 2016; Wheler et al., 2015). Clearly, at least for the vast majority of cancer patients, we have yet to deliver.

Cancer immunotherapy—leveraging the immune system to treat cancer—is an overlapping area showing terrific promise. It has many modalities, one of which is to actively reengineer a patient's immune cells to target tumor-specific antigens, and another of which involves vaccination with "neoantigens," i.e., peptides that are unequivocally unique to the tumor because they arose through somatic mutation. For the latter, a combination of exome sequencing and computational design can be used to generate a set of patient- and tumor-specific epitopes that are predicted to bind MHC class I and induce T cell-mediated immunity. In a recent small-scale study, four of six stage III/IV melanoma patients treated with such immunogenic personal vaccines followed by surgery had no recurrence 25 months post-vaccination, while the two that recurred were effectively treated with checkpoint blockade (Ott et al., 2017). This kind of approach obviously requires testing on larger numbers of patients and more tumor types before its efficacy is proven, but it potentially represents a new genome-centric paradigm for cancer treatment.

The observation that the early detection of many common cancers leads to substantially better outcomes predated the genomic era; this is of course the motivation for screening measures including colonoscopy and mammography. Even for those cancer types for which screens are available, the modest proportion of cases detected when the tumor is localized—less than four in ten colorectal tumors, and about six in ten breast cancers—argues both for the refinement and continued use of existing screening methodologies and for the development of new, minimally invasive biomarkers (Noone et al., 2018). As such, there has been considerable investment over the past decade into the use of DNA as such a biomarker—not just for early detection but also for detection of recurrence, for monitoring response to treatment, and as a companion diagnostic to select appropriate therapies.

Tumors shed DNA, just like a fetus or placenta sheds DNA, into circulation. This circulating tumor DNA (ctDNA) reflects the mutational profile of the tumor: the ensemble of somatic point mutations, copy-number changes, aneuploidy, and other genomic aberrations that distinguish the tumor from the healthy tissue. In the context of late-stage cancer recurrence detection, the presence of disease can be surveilled via the ctDNA in bespoke fashion by first sequencing the patient's tumor, i.e., after a conventional biopsy, to define a list of mutated loci to

follow over time, or in a more generic assay focused on regions commonly mutated across many cancers. Whether either of these approaches will translate to the goal of early detection is less clear, owing to a number of factors. First, the proportion of ctDNA in the circulation is, on average, substantially lower for early, localized tumors than for the late-stage tumors typically monitored in this way (Bettegowda et al., 2014; Haque and Elemento, 2017). Second, the bespoke model is effectively impossible to apply to early detection, and approaches based on lists of the most frequent mutations are inherently limited in their scope. Third, the bar is high for the performance characteristics of a screening test that will be applied to healthy individuals, and appropriately so, as each false positive will incur unnecessary anxiety and expensive follow up. Fourth, some recent studies suggest that for at least some cancer types, metastases may be seeded through early-stage dissemination (Hosseini et al., 2016).

Of course, these reasons for caution are balanced in part by countervailing reasons for optimism. First, any meaningful shift toward earlier detection, even if it falls short of stage I, is likely to improve outcomes for a broad range of cancer types. Second, complementary strategies being developed by us and others involve focusing on epigenetic signals, such as aberrant ctDNA fragmentation or methylation, as additional sources of information that can be used to detect the presence of a tumor and localize it to an anatomical compartment (Guo et al., 2017; Snyder et al., 2016; Sun et al., 2015). Third, even further additional signals, e.g., protein biomarkers, can be combined with information from ctDNA to improve predictive performance (Cohen et al., 2018). Fourth, even further information from the same patient (e.g., monitoring of their immune system, their likelihood of disease based on medical history, other risk factors, or even their PRS for each cancer type), could effectively be used as a prior while interpreting the results of a ctDNA screening test.

Initially, such screens are likely to be focused on detection of a specific type of tumor, for example, measuring promoter methylation of *SEPT9* for colorectal cancer (deVos et al., 2009) or quantifying circulating fragments of the Epstein-Barr viral genome for nasopharyngeal carcinoma (Chan et al., 2017). Indeed, such tests are already in limited clinical use, either in geographic areas with high incidence of a certain cancer or in patient groups reluctant to be screened by more established means. Looking forward, one possible outcome is the development of a pan-cancer (or at least multi-cancer) screen capable of simultaneously detecting and localizing a large number of tumor types at early stage. Even a partial achievement of this goal has the potential to radically change the way that we screen for cancer.

The Future of Genomic Medicine

Amidst the excitement around the HGP, there was perhaps a naive hope that the human genome would somehow magically solve everything. It obviously has not—but it is having an impact. We have gone from sequencing one human genome to over a million, with tens of millions more genotyped, in just 15 years. We have a more grounded understanding of the complexities of the genetic component of common disease risk, including the roadblocks between association signals and the development of meaningful therapies. We have a vastly more comprehensive catalog of the molecular lesions underlying cancer and can apply "precision therapies" in as many as half of patients, albeit only to be stymied in nearly all cases by cancer's remarkable ability to evolve. We are on the path to understanding the genetic basis of nearly all Mendelian disorders and to making meaningful impacts on the lives of those patients through diagnoses and, for at least a small subset of patients, through cures. In retrospect, the initial expectations were clearly set too high. But at the same time, what we have accomplished, and the trajectory that we are on as a field, are nothing to sneeze at. Furthermore, in certain areas (e.g., the cost of sequencing, NIPT, Mendelian disease), the field has advanced much more quickly than anyone anticipated.

We should not shy from setting high expectations, but one concern about promising aggressive timelines for therapies and cures is that it results in an excessive focus on often-unrealistic short-term objectives, which is in turn a disservice to the longer journey that this inevitably will be. Furthermore, as NGS, genome editing, and other breakthroughs clearly show, the human genome sequence is not enough, and achieving maximal impact for our field demands that we expand our investment in basic science, foundational resources, and technologies that are designed and calibrated to serve the long-term view. Grand challenges for the future of the genome sciences that we are particularly excited about in the sense that we think that they could serve to accelerate progress across the board, include (1) understanding, at least at some basic level, the function of every gene in the human genome; (2) scaling the identification of causal variants, genes, and mechanisms for existing GWAS signals from a handful to thousands; (3) a spatially resolved molecular atlas of all human cell types, from birth to death, e.g., including their chromatin landscape, gene expression, and protein expression signatures; and (4) developing accurate, quantitative models for predicting the impact of arbitrary sequence variants on gene expression and/or protein function in any one of these cell types. A fuller list of potential grand challenges for both genome sciences and genomic medicine in the coming decade is shown in Figure 4.

We are well along the path to a future in which a substantial fraction of the human population, at least in the developed world, will have their genomes genotyped or sequenced, and where that information is available together with their electronic healthcare records for both clinical and research uses (Topol, 2014). The phenotypes to which many of these genomes are linked will outgrow the conventional medical record, e.g., longitudinal molecular profiles and imaging, recording of activity and exposures, etc. Sequencing in some form is likely to become routine for all cancers and possibly for prospective parents and the unborn as well. We may even be recurrently sequenced, e.g., routine monitoring of cfDNA for cancer or other conditions. Finally, we have focused here on human genomes, but the genomes of commensal and pathogenic microorganisms are likely to be routinely interrogated as well.

Much of the value of an individual's genetic information lasts throughout their lifetime, meaning that advances in our ability to interpret variation will continue to provide benefits. Although genome sequencing may only have marginal benefits for many if not most patients, the improved understanding of human

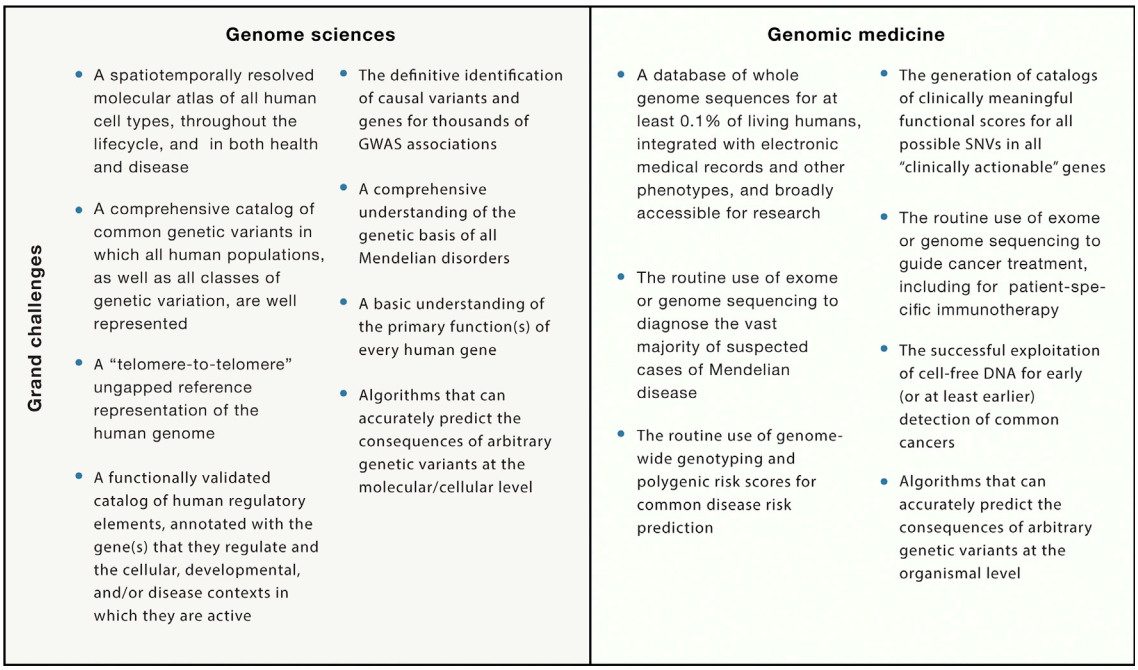

Figure 4. Future Grand Challenges for Genome Sciences and Genomic Medicine
A selection of future grand challenges for the genome sciences (left) and genomic medicine (right).

biology that comes from conducting genetics on humans will have an impact that lasts as long as our species does. Combined with other advances (e.g., PRSs, gene therapy, immunotherapy, etc.), our collective genomes will serve as a basis not only for advancing our understanding of disease but also for the development of new preventative and therapeutic strategies.

At some level, we worry that the above framing is again setting high expectations, so we should be clear. We continue to believe in the transformative potential of genomics on medicine and argue that the progress of the last 15 years, although poorly aligned with oft-criticized predictions made in the past, provides more-than-ample evidence to support this potential. At the same time, the reality will be nuanced, and there are no guarantees here. Large hurdles remain, and continued investment in basic science and technology is unquestionably necessary to overcome them. In our view, much of the biomedical research enterprise, including genomics, should be thought of as long-term bets for our society and our species, investments whose payoffs may not be fully realized for many decades or even in our lifetimes. That does not make these investments any less worthwhile.

In closing, we note that the Human Genome Project was accompanied by an early recognition of the ethical, legal, and social implications (ELSIs) that it would raise. These concerns have never been more paramount. We are increasingly identifiable, even if we have never volunteered our own DNA, through the combination of proliferating ancestry tests and pedigree searches (Erlich et al., 2018). Scientific racism, which continues to misappropriate studies of human genetics, is alive and well. Individual scientists have flaunted norms, and perhaps laws, to perform medically unnecessary genetic modifications to the human germline (Belluck, 2018). The life insurance industry has taken a strong interest in PRS (Russell, 2018), while US-based startup companies purport to offer embryo selection for non-disease traits (Belluck, 2018; Wilson, 2018). As we grapple with these and other ethically and socially alarming developments, it is incumbent on our field to much more proactively assume responsibility not only for maximizing the benefits associated with the human genome and genomic medicine but also for minimizing the harms.

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DECLARATION OF INTERESTS

J.S. has financial interests in companies working on subjects related to genomic medicine, including Adaptive Biotechnologies, Bellwether Bio, Camp4 Therapeutics, Cambridge Epigenetix, GenePeeks, Maze Therapeutics, Nanostring, Phase Genomics, and Stratos Genomics. His lab has an unfunded collaborative research agreement with Illumina. M.W.S. is a founder and employee of Bellwether Bio.

SUPPORTING CITATIONS

The following references appear in Figure 2: Lynch et al. (2004); Margulies et al. (2005); Ozaki et al. (2002); Sahin et al. (2017); Shendure et al. (2005).

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