GENOMICS

Genomic Medicine: A Decade of Successes, Challenges, and Opportunities

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Genomic medicine—an aspirational term 10 years ago—is gaining momentum across the entire clinical continuum from risk assessment in healthy individuals to genome-guided treatment in patients with complex diseases. We review the latest achievements in genome research and their impact on medicine, primarily in the past decade. In most cases, genomic medicine tools remain in the realm of research, but some tools are crossing over into clinical application, where they have the potential to markedly alter the clinical care of patients. In this State of the Art Review, we highlight notable examples including the use of next-generation sequencing in cancer pharmacogenomics, in the diagnosis of rare disorders, and in the tracking of infectious disease outbreaks. We also discuss progress in dissecting the molecular basis of common diseases, the role of the host microbiome, the identification of drug response biomarkers, and the repurposing of drugs. The significant challenges of implementing genomic medicine are examined, along with the innovative solutions being sought. These challenges include the difficulty in establishing clinical validity and utility of tests, how to increase awareness and promote their uptake by clinicians, a changing regulatory and coverage landscape, the need for education, and addressing the ethical aspects of genomics for patients and society. Finally, we consider the future of genomics in medicine and offer a glimpse of the forces shaping genomic medicine, such as fundamental shifts in how we define disease, how medicine is delivered to patients, and how consumers are managing their own health and affecting change.

INTRODUCTION

This year marks the 10th anniversary of the official completion of the Human Genome Project, a project that enabled the systematic exploration of the molecular underpinnings of disease and generated expectations of the transformation of medicine. Although the previous decades were marked by improvements in overall health and longevity, before completion of the Human Genome Project, the tools used for diagnosis and treatment of disease were often blunt and imprecise. Most diseases were defined by anatomical location and clinical symptoms and treated with one-size-fits-all therapies that failed to account for the unique biological background of the individual. Despite the development of rational drug design strategies, therapeutic efficacy has remained unacceptably low (*1*).The Human Genome Project laid the foundation for genomic medicine, offering a means of defining disease at the molecular level. Along with advances in genotyping and sequencing technologies, bioinformatics, systems biology, and computational biology, the fruits of the Human Genome Project have fueled important biological discoveries at an unprecedented rate. Today, genomic medicine aims to build on this foundation, translating these discoveries into clinical practice, with the ultimate goal of personalized medicine.

This State of the Art Review highlights the latest achievements in genome research and their impact on medicine, primarily in the past decade. In some cases, genomic discoveries have led to marked changes in the clinical care of patients. However, the transition to genomic medicine has not been smooth, and many challenges still exist. We explore these challenges and discuss innovative solutions. Finally, we contemplate the future, offering a glimpse of the expected changes in health care as genomic medicine takes hold.

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GENOMIC MEDICINE SUCCESSES

The term "genomic medicine" was virtually absent from our lexicon before 1995; now, it permeates the medical literature, the press, and the economy. The Human Genome Project resulted in the launch of thousands of biotechnology firms globally and the development of faster and cheaper technologies for querying the genome, which have fueled discoveries of disease biomarkers and drug targets. The pharmaceutical industry has adopted genome-enabled drug discovery, and the market for molecular diagnostics has grown rapidly. There are now groundbreaking examples of the application of genomics across the stages of disease, from risk stratification and screening to diagnosis and prognosis to treatment (Table 1). For some diseases like breast cancer, HIV infection, and chronic hepatitis C virus (HCV) infection, genome-based tools have been woven into clinical practice and disease management (Fig. 1), but for most areas of medicine, the uptake of genomics has been slow.

SEQUENCING TECHNOLOGY: THE DRIVER OF GENOMIC MEDICINE

Technology has been an enabling force, providing transformative tools for genomic research including genome-wide association studies (GWAS) and next-generation sequencing (NGS). In 2005, GWAS made their debut with the identification of a major susceptibility gene for a complex trait. Through evaluation of hundreds of common genetic variants, Klein *et al.* identified mutations in the complement factor H gene as a genetic cause of age-related macular degeneration

Table 1. Examples of genomic tests used in clinical practice.

Susceptibility to common diseases
BRCA1/BRCA2 for breast and ovarian cancer predisposition
Lynch syndrome genetic screening in colorectal cancer families
Human leukocyte antigen (HLA) typing to aid in diagnosis of celiac disease
***NGS for Mendelian disorders and diagnostic dilemmas**
***NGS for noninvasive prenatal screening/diagnosis**
Preclinical diagnosis and prognosis
Oncotype DX: 21-gene RNA signature for breast tumors; 12-gene RNA signature for colon tumors
MammaPrint: 70-gene RNA signature for breast tumors
OVA1: 5-protein signature for ovarian mass malignancy
AlloMap: 11-gene (blood RNA) signature for monitoring rejection after cardiac transplant
Corus CAD: 23-gene (blood RNA) signature for coronary artery disease
Cancer pharmacogenomics
HER-2—trastuzumab
EGFR—gefitinib
KRAS—cetuximab and panitumumab
ALK—crizotinib
BRAF—vemurafenib
Pharmacogenomic dosing
CYP2D9/VKORC1—warfarin
Pharmacogenomic adverse events
*HLA-B*5701*—abacavir (HIV infection)
*HLA-B*1502*—carbamazepine (epilepsy, bipolar disorder)
Pharmacogenomic efficacy
CYP2C19—clopidogrel (coronary artery disease, peripheral vascular disease)
IL28B—pegylated interferon/ribavirin (HCV infection)

*NGS, next-generation sequencing.

(*2*). Notwithstanding its limitations, including its restriction to common variants, incomplete genome coverage, and inherent challenge of discerning the actual causal genetic variant, GWAS has been a transformative technology, representing a major advance over the one-gene-at-a-time candidate gene approach used for decades before. Moreover, GWAS provided an indirect means of querying common genetic variation across the entire human genome in an unbiased fashion, offering an unprecedented opportunity to uncover new biological pathways of disease.

From 2001 to 2012, the cost to sequence a human genome dropped from $100 million to less than $10,000, and these costs continue to decline (*3*). Current sequencing machines can read about 250 billion bases in a week compared to only about 5 million in 2000 (*4*). NGS technology (also known as massively parallel sequencing) now allows direct measurement of not just common variants but theoretically all variation in a genome (*5*). Data from the 1000 Genomes Project have confirmed previous estimates of the population frequency of germline variants to be about 1 in every 1000 of the 3.2 billion nucleotide positions, giving rise to about 3 million variants in the human genome (*6*). The effect of genetic variants in the ~1% of the genome that codes for genes is somewhat predictable. The challenge lies in figuring out the meaning of variants that occur in the vast remaining noncoding regions of the genome, the so-called dark matter, whose function is largely unknown. Consequently, the National Human Genome Research Institute initiated project ENCODE, the Encyclopedia of DNA Elements, whose goal is to functionally annotate noncoding regions of the genome (*7*). This ongoing initiative will provide new insights into the organization and regulation of genes throughout the genome, enhancing the ability to annotate variants of unknown significance.

In the interim, researchers have focused on exome sequencing, which examines variation in the coding sequence (genes), where mutations have predictable effects on downstream protein structure. Individuals typically carry several hundred rare and potentially deleterious coding region variants (*6*). For rare, Mendelian disorders, those controlled by a single gene with a simple pattern of inheritance, the variants found in as few as one or two affected individuals can be compared to those found in unaffected individuals to pinpoint disease-causing mutations. The first successful applications of exome sequencing came in 2009 with the diagnosis of patients with Freeman-Sheldon syndrome (*8*), Miller syndrome (*9*), and congenital chloride diarrhea (*10*). These and other Mendelian disorders, with their relatively simple genetic basis, are amenable to exome sequencing of their DNA and the DNA of a small number of other affected or unaffected individuals.

Today, GWAS and NGS are integral tools in basic genomic research, but are increasingly being explored for clinical applications, including the clinical diagnosis of rare genetic diseases (*11*), the selection of cancer treatments based on molecular characterization of the tumor (*12*), and the tracking of infectious disease outbreaks in real time (*13*). Elucidating the genetic basis of common diseases has been more challenging, but research in this area has broadened our understanding of underlying disease mechanisms and has revealed new therapeutic approaches through repurposing of existing drugs for treating diseases they were not originally intended to treat (*14*–*16*).

TUMOR SEQUENCING FOR CANCER PHARMACOGENOMICS

One of the most high-profile disease areas to benefit from NGS is cancer. All cancers arise as a result of DNA mutations, which confer a growth advantage upon the cells in which they have occurred, giving rise to tumors. Comparison of the genetic profiles of tumors and the surrounding normal tissue can reveal the acquired changes driving growth that may be targets for treatment. Meanwhile, comparisons across patients and tumor types are changing how cancers are classified and treated.

Targeted therapies for cancer

The idea of pairing medicines with specific tumor markers in a targeted fashion to improve efficacy of cancer therapies is not new. In the mid-1980s, detailed molecular studies of breast tumors led to the discovery of HER-2, a biomarker overexpressed in about 30% of breast tumors and associated with adverse outcomes (*17*). HER-2 typing of primary breast tumors provided clinicians with a new tool that could be used to guide adjuvant chemotherapy (*18*). The development of trastuzumab (Herceptin) in 1998, a humanized monoclonal antibody targeting HER-2, resulted in widespread adoption of the HER-2 test

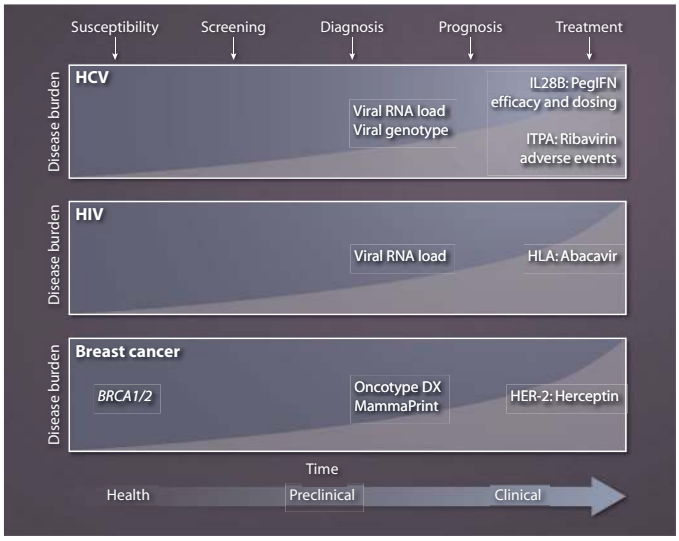

Fig. 1. Genomic medicine in action. Examples of three conditions where genomic medicine tools and information have affected clinical management at various stages of disease. (Top) In chronic HCV infection, several genomic markers are used in disease management: viral RNA concentrations are used for diagnosis and monitoring; the genotype of the virus is used for prognosis and treatment response; and host *IL28B* and *ITPA* genotypes are used as pharmacogenomic markers for efficacy and dosing. (Middle) In patients infected with HIV, viral RNA concentrations are used for diagnosis and monitoring, and host *HLA* genotype is used as a pharmacogenomic marker of hypersensitivity to abacavir treatment. (Bottom) In breast cancer, germline *BRCA1/BRCA2* genotyping is used to determine susceptibility to breast and ovarian cancer; analysis of tumors with Oncotype Dx or MammaPrint is used to predict likelihood of recurrence; and expression of the tumor marker HER-2 is used to inform treatment with the monoclonal antibody Herceptin.

(*19*), now part of the standard workup and management of breast cancer (*20*–*22*) (Fig. 2). During the following decade, other examples of cancer therapies with companion diagnostics emerged (Table 1). The introduction of *EGFR* mutation testing has markedly improved the efficacy of gefitinib and erlotinib, small-molecule drugs for the treatment of non–small cell lung cancer that target epidermal growth factor receptor (EGFR) (*23*, *24*). In metastatic colorectal cancer, tumors with mutated *KRAS* are almost always resistant to treatment with cetuximab and panitumumab, leading the American Society of Clinical Oncologists and the U.S. Food and Drug Administration (FDA) to recommend withholding the drugs in these patients (*25*, *26*). With the introduction of NGS, researchers and clinicians can now make a comprehensive assessment of tumor markers, increasing the rate of discovery of new targets, new therapeutic alternatives, and new clinical management guidelines for cancer treatment. In 2011, two cancer drugs received accelerated approval by the FDA for use with a companion diagnostic test: crizotinib for the treatment of patients with locally advanced or metastatic non–small cell lung cancer with its companion diagnostic designed to detect the *EML4-ALK* fusion gene (*27*) and vemurafenib for the treatment of patients with metastatic or unresectable melanoma positive for *BRAF* V600E mutations (*28*).

More recently, NGS of tumors has identified the existence of the same mutations in distinct cancer types, prompting the expansion of indications for some FDA-approved drugs. *BRAF* V600E mutations not only are common in melanoma but also have been widely observed in other cancers (*29*), especially hairy cell leukemia (*30*), leading to the expanded use and ultimate demonstration of vemurafenib as a viable treatment option for refractory hairy cell leukemia (*31*). Similarly, early studies indicate that crizotinib, targeting *EML4-ALK*–positive non–small cell lung cancers, is effective against other types of tumors containing *ALK* alterations, such as aggressive forms of pediatric neuroblastoma and anaplastic large cell lymphoma (*32*). As the field progresses, the way tumors are classified is shifting away from tissue of origin and toward molecular taxonomy, having a profound impact on the manner in which treatment decisions are made.

Tumor genome analysis is also being explored in cancer patients to identify new markers and mechanisms of drug sensitivity or resistance. By sequencing the tumor of a patient with durable remission of metastatic bladder cancer after treatment with everolimus, Iyer *et al.* identified a loss-of-function mutation in *TSC1* as a marker of everolimus sensitivity (*33*). Similarly, patients with non–small cell lung cancer treated with crizotinib are prone to relapse, leading to the development of next-generation ALK inhibitors to overcome crizotinib resistance. Genomic alterations in resistant tumors were found to correlate with response to these newer therapies, providing the rationale for pursuing targeted combinatorial therapeutics to combat resistance (*34*).

NGS of tumors is not without its limitations (*35*). Tissue sampling is problematic: The limited availability of tissue from a standard biopsy, the need for fresh (as opposed to preserved) tissue, the inherent heterogeneity within a tumor, the presence of aneuploidy, and the contamination of tumor samples with surrounding normal tissue all affect the ability to comprehensively characterize tumor mutations. Further computational and experimental approaches are required to distinguish those mutations responsible for cancerous growth (drivers) from those that are inconsequential (passengers). The International Cancer Genome Consortium (https://www.icgc.org/icgc) and the Cancer Genome Atlas (http://cancergenome.nih.gov/) represent international collaborative efforts to define the spectrum of mutations found in tumors, mapping the genomic landscape of cancer. These efforts will provide a foundation from which to develop therapeutic strategies against new targets, but this process is not trivial and, even when successful, may be short-lived as therapeutic resistance evolves. Thus, whereas NGS is a promising new tool, it is not a panacea for cancer genomic medicine.

Circulating tumor markers

Another noteworthy application of NGS is noninvasive cancer detection, either in the setting of primary diagnosis or in monitoring recurrence after treatment. Leary and colleagues have laid the groundwork for this, demonstrating that chromosomal rearrangements, a hallmark of cancerous tumors, can be detected in blood samples from cancer patients using NGS (*36*). This method is successful at discriminating samples from cancer patients from those of healthy controls, but the sensitivity and specificity depend highly on the amount of tumor DNA present in the sample and the detection limits of the sequencing technology (*37*). This method shows promise for monitoring tumor burden to determine response to treatment, providing an alternative to serial radiographic imaging, which often fails to detect changes in tumor burden. In metastatic breast cancer, Dawson and colleagues demonstrated marked improvements in detection of chromosomal rearrangements as markers of tumor burden, over and beyond specific cancer antigens or generic circulating tumor DNA (*38*). Improvements in NGS technology will only enhance the ability to detect and monitor cancer, with the potential to markedly alter how the disease is managed.

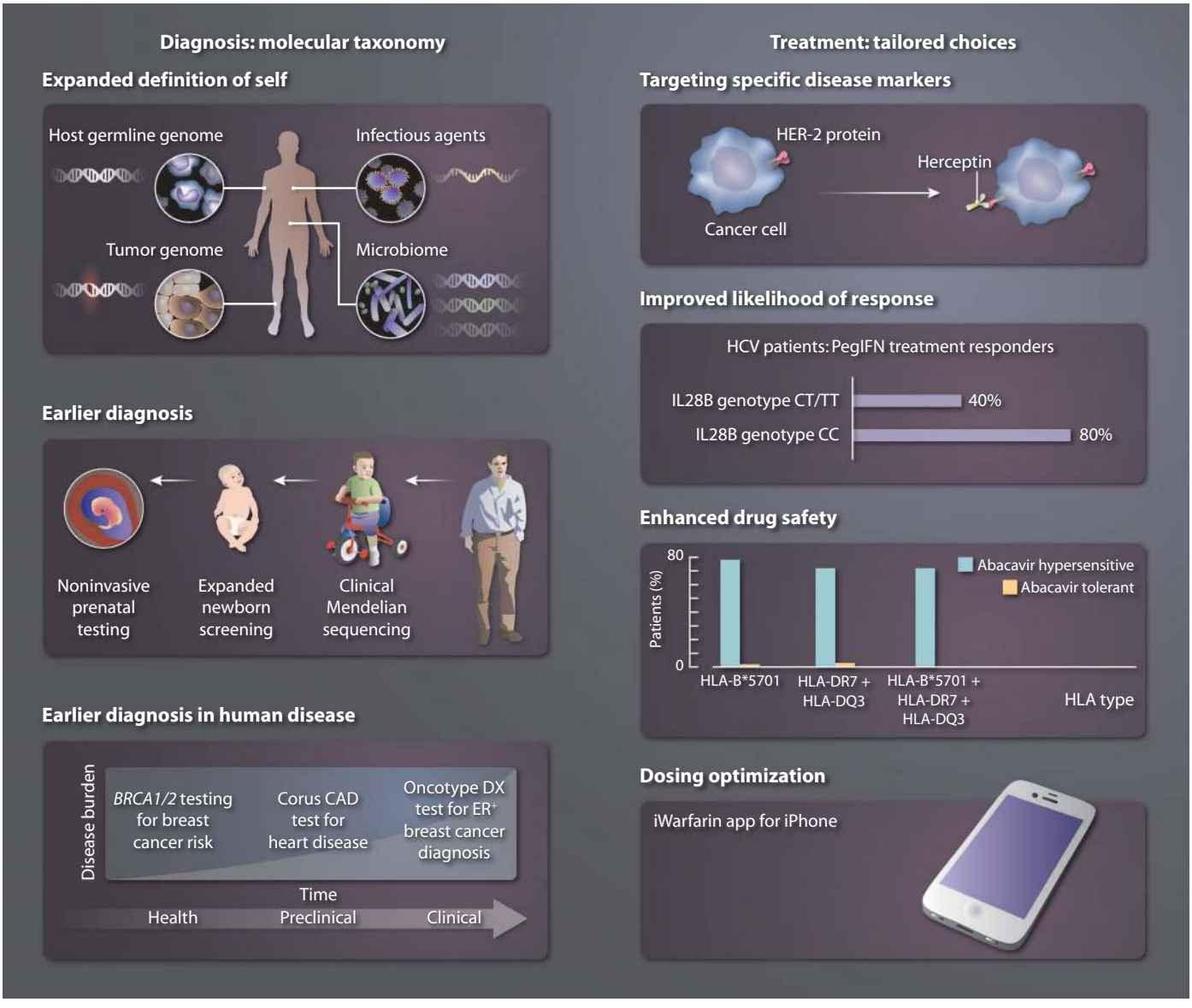

Fig. 2. Trends in genomic medicine. Several themes are emerging in the diagnosis and treatment of disease. (Left) First, as the knowledge of the genomic underpinnings of disease increases, the definition of "self" is likewise expanding. This self includes not just the germline human genome inherited from our parents but also somatic changes in the genomes of tumors, the genomes of commensal microbes that inhabit our body, and the genomes of pathogenic organisms. Second, the influence of genomics on medicine is moving the diagnosis of diseases toward the earliest possible point in the course of disease, before clinical manifestation. Third, genomic testing is occurring earlier in the life of a human, moving from adulthood to childhood, the neonatal period, and even prenatally. (Right) Pharmacogenomic markers are being used in several ways: to select targeted therapies exemplified by the breast cancer marker HER-2 and treatment with the monoclonal antibody Herceptin; to predict likelihood of response, as in the case of the host *IL28B* genotype and response to interferon therapy in HCV infection; to enhance drug safety, for example, by testing for host HLA genotypes predictive of abacavir hypersensitivity in humans infected with HIV; and to optimize dosing of drugs, such as warfarin, based on genotypes indicative of rate of metabolism using, for example, the iWarfarin app.

CLINICAL SEQUENCING AND DIAGNOSTIC DILEMMAS

According to the Online Mendelian Inheritance in Man database (http://omim.org/), about 3676 Mendelian disorders have a known molecular basis. However, there are nearly as many suspected Mendelian traits for which the molecular basis remains to be identified. The potential for clinical sequencing to find the underlying cause and identify treatment options for these rare, debilitating diseases has led to the formation of various large national and international consortia. In the United States, three Centers for Mendelian Genomics have been established at the University of Washington, Yale University, and a joint Center at Baylor College of Medicine and Johns Hopkins University (*39*). Moreover, clinical sequencing is being offered to patients with unknown yet suspected genetic diseases, the so-called diagnostic

dilemmas, at many major medical centers and through programs such as the National Human Genome Research Institute's Undiagnosed Diseases Program (http://www.genome.gov/27544402). One notable case from the Medical College of Wisconsin involved the use of clinical exome sequencing to identify a gene variant in a child who presented to the clinic with a severe, intractable form of inflammatory bowel disease for which physicians were unable to provide a diagnostic explanation (*40*). The discovered variant in the *XIAP* gene defined a new form of inflammatory bowel disease due to deficiency of an X-linked inhibitor of apoptosis. Knowledge of the causal mutation led to a cure through allogeneic bone marrow transplantation and demonstrated the power of clinical NGS as a strategy for diagnosis and management of rare diseases. Early results from a number of clinical sequencing programs estimate the success rate of disease gene identification at about 50%, offering hope to thousands of individuals with previously undiagnosed or untreated rare disorders (*41*, *42*).

Newborn screening, prenatal diagnosis, and preconception carrier testing

A natural outcome of identifying genes for rare Mendelian disorders is the application of these findings to earlier detection, either at birth (newborn screening), in utero (prenatal diagnosis), or preconception (carrier testing). Newborn screening is a mandatory, state-supported public health program meant to protect newborn children by screening them for rare, treatable (and thus preventable) disorders at birth. The scope of diseases tested varies by state but has been steadily increasing from an average of 5 conditions in 1995 to a uniform panel of 31 core disorders and 26 secondary disorders currently recommended by the U.S. Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (*43*). Some states evaluate additional conditions, including diseases that affect children at a later stage in development and others for which the benefits of early intervention are limited. The number of conditions considered for newborn screening will undoubtedly grow with genome sequencing, improving early diagnosis. A concern is that, as a consequence, expanded screening will erode the ethical justification for this compulsory program and may undermine one of the most successful public health programs in existence (*44*).

Prenatal diagnosis moves screening for genetic disorders even further upstream by detecting genetic variation in the developing fetus. Traditionally, fetal DNA is obtained invasively through amniocentesis or chorionic villus sampling, but a potential alternative emerged in 1997 when it was demonstrated that cell-free fetal DNA circulates in maternal blood and could be isolated, amplified, and sequenced noninvasively through a sample of maternal plasma (*45*). In 2008, NGS technologies were used successfully for the first time to identify fetal aneuploidy from cell-free fetal DNA in maternal plasma (*46*, *47*). Clinical trials of the new method rapidly followed, and by late 2011, noninvasive prenatal testing of trisomy 21 by sequencing of maternal plasma DNA was being offered on a clinical and commercial basis in the United States and China (*48*). In the third quarter of 2012, Sequenom Inc., one such company offering this test, had reached a 90,000 annualized test volume run rate for the MaterniT21 PLUS test (*49*).

Noninvasive prenatal testing for disorders caused by large deletions, single-nucleotide substitutions, and other types of genetic variation, as opposed to de novo chromosomal aneuploidies like trisomy 21, is more challenging due to the fact that maternal plasma contains DNA from both the fetus and mother, who may share the same mutation. However, progress has been made in this area as well (*50*, *51*). Investigators at Stanford University applied noninvasive prenatal testing to detect a large genetic deletion underlying DiGeorge syndrome in a first-trimester fetus using only a blood sample from the mother (*52*, *53*). Noninvasive prenatal testing eliminates the need for invasive procedures while also greatly expanding the number of genetic variants that have traditionally been detected in utero.

Even before conception, carrier screening enables couples who are planning a family to assess their risk of having a child with a recessive Mendelian disorder and use this information to guide their reproductive decisions. There are more than 1000 rare, recessive Mendelian disorders for which the underlying genetic mutation is known (*54*). Although individually rare, Mendelian disorders can have a sizable public health impact. Population-based carrier screening for Tay-Sachs disease has reduced the incidence of the disease in Jewish populations in the United States and Canada by more than 90% (*55*). Considering that each person is estimated to carry on average 2.8 mutations for known severe recessive disorders (*56*), the impact of screening could be sizable in terms of reduced disease morbidity and mortality in the population. The impact could be particularly significant in populations such as Ashkenazi Jewish, who are disproportionately affected by recessive disorders. There may also be utility for screening in the setting of in vitro fertilization, where preimplantation genetic analysis has the potential to reduce the incidence of disease. Panels of tests for hundreds of childhood recessive illnesses with severe clinical manifestations have been developed (*56*), and some are offered directly to patients through companies such as Counsyl Inc.

Genetics of common complex diseases

Unlike rare Mendelian disorders, the genetic dissection of common, complex diseases such as cancer, cardiovascular disease, and diabetes has proven to be more difficult. These diseases by definition are due to the complex interplay of many gene variants, both common and rare, as well as nongenetic factors. GWAS, the current method used to find these genes, has been carried out on large cohorts of patients and controls across numerous traits and diseases, revealing hundreds of common genetic variants associated with those traits (http://www.genome.gov/gwastudies). Researchers are now turning to NGS to identify rare genetic variants associated with complex diseases. For example, exome sequencing in neurodevelopmental conditions has identified de novo mutations linked to diseases like autism and schizophrenia (*57*). However, exome sequencing of large numbers of subjects with a complex trait can be costly and experimentally challenging (*58*). Often, thousands of patients are required to assign statistical significance to rare variant associations with complex diseases. Innovative study designs such as exome sequencing of patients with extreme phenotypes have yielded some successes, including the identification of *DCTN4* associated with clinical sequelae in cystic fibrosis patients infected with *Pseudomonas aeruginosa* (*59*).

Despite the unequivocally strong statistical associations between genetic variants and complex diseases, their low sensitivity and specificity afford limited clinical value for disease predisposition testing. Notable exceptions include genes underlying breast cancer (*60*), Lynch syndrome (*61*), and celiac disease (*62*), where some variants have enabled prophylactic treatment or screening of other family members, which may provide cost-effective alternatives to standard disease management strategies.

Amidst myriad technological advances and gene discoveries, a simple family history continues to be advocated as a tool for identification of common disease risk. For very common conditions with high heritability, such as cardiovascular disease, family history is a much stronger predictor of disease than any single or combination of genetic/genomic markers (*63*). One model suggests that neither family history nor genetic testing should be used as a standalone but that the real power for disease prediction, risk assessment, and differential diagnosis comes from their combined use (*63*).

Pharmacogenomic markers

GWAS approaches have also been used successfully in pharmacogenomics research. Several markers of efficacy, adverse events, and dosing of therapeutics have been found, but their uptake into clinical practice is variable, despite the clear actionability of these types of variants. In some cases, such as with the *HLA-B*5701* genotype for the HIV drug abacavir (*64*) and *HLA-B*1502* for the antiseizure drug carbamazepine (*65*), carriers of these genotypes should avoid the drug entirely to eliminate a specific serious adverse event. In other cases, such as *TPMT* for mercaptopurine (*66*) or *CYP2C9*/*VKORC1* for warfarin (*67*, *68*), adjusting the dose of drug based on genotype can help to avoid toxicity and improve efficacy. Actionability is not enough to ensure uptake of pharmacogenomic testing. Such is the case with the antiplatelet drug clopidogrel, where despite having an FDA "black box warning" for efficacy in individuals carrying the *CYP2C19* genetic variant, there is no clear consensus among physicians on its use (*69*). In hepatitis C treatment, on the other hand, the *IL28B* genotype test not only has proven to be highly predictive of response to pegylated interferon/ribavirin used to treat chronic HCV infection but also has seen rapid and widespread adoption in the clinic (*70*). Genetic markers that predict reduced therapeutic efficacy may face a high hurdle for established drugs, unless evidence supporting clinical validity and utility of the test is indisputable.

Drug repurposing

Among the new programs at the National Center for Advancing Translational Sciences (http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/rescue-repurpose.html) is one aimed at using genomic information to determine whether drugs approved to treat one disease may be effective in treating others. With 6% of the genome already being pursued for targets of therapy development (*14*), additional investigations into the phenotypes associated with variation in these targets may open the door to expanded indications. Indeed, two different researchers recently demonstrated the feasibility of using genomic information to repurpose drugs. They used computational analysis to compare gene expression profiles characteristic of certain diseases with profiles characteristic of specific drugs. By searching for complementary patterns of gene expression, they successfully identified new disease-drug matches, including a match between the antiulcer drug (cimetidine) and lung cancer (*15*) and a match between the antiepileptic drug (topiramate) and inflammatory bowel disease (*16*), and validated their predicted use in vivo in rodent models.

Another group used GWAS data for drug repurposing (*14*). Disease genes uncovered through GWAS are 2.7-fold enriched for the molecular targets being pursued by drug developers (*14*). Besides the expected overlap in GWAS genes and drug targets for the same clinical indication (trait), Sanseau and colleagues uncovered more than 100 drug targets that were associated with traits not considered as a primary indication, opening the door for drug repurposing. In one example, GWAS identified *TNFSF11* variants associated with Crohn's disease. *TNFSF11* is the target for the monoclonal antibody denosumab, currently marketed for osteoporosis, but as a result of this research, it may also be considered for Crohn's disease. Repurposing of existing FDA-approved drugs eliminates the need for lengthy clinical trials because formulation, dosing, and safety have already been worked out, offering new avenues of treatment for these conditions in a short time frame. Even for drugs in development, knowledge of potential expanded indications may provide more impetus to push these drugs through development. Nonetheless, the practicalities of renavigating the many safety and efficacy regulatory hurdles should not be underestimated.

Complex multimarker genomic tests for disease diagnosis and prognosis

Beyond DNA sequence, measures of gene expression, proteins, metabolites, and epigenetic changes are being used to generate comprehensive profiles of biological systems in health and disease. Many of the computational challenges of analyzing these large complex data sets are being addressed to yield next-generation biomarkers that are multianalyte, diagnostic, prognostic, and predictive. There are a growing number of marketed tests that are in vitro diagnostic multivariate index assays (IVDMIAs), which typically measure protein or RNA levels, often with complex algorithms, enabling diagnosis and prognosis (Table 1) (*71*). One example is Oncotype Dx (Genomic Health Inc.), a test that examines expression of 21 genes in tumor tissue to determine the likelihood of disease recurrence in women with early-stage hormone estrogen receptor–positive breast cancer (Fig. 2). The test analyzes expression levels and converts them to a recurrence risk score, which has been shown to help guide treatment in patients, reduce overall health care costs, and improve outcomes (*72*–*75*) and is currently covered by many major insurance companies. Other examples include MammaPrint (Agendia Inc.), which analyzes the expression of 70 genes to determine whether patients are at high or low risk of breast cancer recurrence, OVA1 (Vermillion Inc.), a five-protein test that gauges whether a woman's ovarian mass is malignant and requires surgery, AlloMap (XDx Expression Diagnostics Inc.), an 11-gene blood RNA signature for monitoring rejection after cardiac transplant, and Corus CAD (CardioDx Inc.), a 23-gene blood RNA signature to screen for obstructive coronary artery disease.

Despite their complexity, IVDMIAs like these are finding their way to the market and to the clinic. According to 2007 draft guidance from the FDA (*76*), IVDMIAs are being used to make critical health care decisions and thus should be regulated by the FDA, leading some diagnostic developers to work with regulators preemptively. Some, but not all, of the marketed IVDMIAs have demonstrated analytical and clinical validity, but evidence of clinical utility is almost always lagging (*77*, *78*). Moreover, the very nature of IVDMIAs presents challenges to insurers, who grapple with not only limited data on clinical utility but also how to reimburse such tests that are composed of both a laboratory component and an associated algorithm, used to score risk, the latter part being integral to realizing the test's value (*79*).

The success of some IVDMIAs is a testament not only to the power of computational biology but also to the importance of advocacy and financial resources that the commercial developers of these tests bring to the table. Companies developing IVDMIAs are able to finance pivotal studies aimed at demonstrating clinical validity, navigate regulatory hurdles, advocate for coverage by insurance companies, and disseminate

their tests through marketing to health care providers. Their efforts offer valuable lessons on the effective translation of genomic tests to medicine.

Genomics to assess microbial friends and foes

Another exciting area of genomic medicine involves sequencing the genomes of microorganisms, both the commensal bacteria that regularly inhabit our bodies (the human microbiome) (*80*) and the infectious agents that cause acute and sometimes fatal diseases (*81*). This past year, the Human Microbiome Project published the first results of its study of the microbial populations inhabiting various human body sites (*82*). Besides providing reference sequences for many taxa, the major findings from the analysis of this healthy cohort included correlation of groups of organisms with host characteristics including ethnicity, age, and body mass index. Further research in this area has begun to uncover relationships between human microbial communities and diseases such as diabetes, asthma, psoriasis, atherosclerosis, obesity, and others (*83*, *84*). In one example, the gut microbiome has been linked to inflammatory bowel disease, with patients showing dysbiosis of their gut microbiome, specifically an expansion of the Proteobacteria phylum that may lead to inflammation (*85*). This study, along with others from GWAS showing that patients with inflammatory bowel disease bear polymorphisms of genes conferring gastrointestinal innate immunity, has led investigators to implicate host immune responses to Proteobacteria in the etiology of inflammatory bowel disease (*86*). Moreover, strategies to modify the gut microbiome are being explored as treatments for inflammatory bowel disease, including the use of fecal microbiota transplantation or engraftment of microbiota from a healthy donor into a recipient (*87*). The burgeoning study of the human microbiome holds tremendous promise for personalized medicine because microbial composition can be altered noninvasively through diet or the use of probiotics or antibiotics.

In the area of infectious disease, NGS of pathogenic microorganisms can supplant the need to first grow them in culture, previously a major impediment to pathogen identification. For example, in 2003, sequencing of samples from infected patients with the severe acute respiratory syndrome (SARS) allowed investigators to identify the causative agent as a coronavirus (*88*). Comparison of sequences of multiple isolates of an organism from a single epidemic gives a picture of the organism's evolution, allowing one to infer where the outbreak began and how the infection spread. Sequencing was used to determine the origins of historical outbreaks of cholera (*89*), tuberculosis (*90*), and the 2009 H1N1 influenza outbreak as well (*91*). Similarly, the source of carbapenem-resistant *Klebsiella pneumoniae* in a recent hospital outbreak was identified by sequencing isolates of the bacteria from infected individuals and examining the genetic differences (*92*). From these data, scientists were able to determine the chronology of infection, the likely silent carriers who transmitted the infection, and the hospital equipment that may have acted as a reservoir for the bacteria, even after standard decontamination procedures. The genomic analysis was also able to pinpoint when resistance to carbapenem first developed. The ability to sequence microorganisms in a clinically relevant timeframe means that these methods can now be applied in real time. For example, an outbreak of methicillin-resistant *Staphylococcus aureus* was recently curtailed in a hospital after applying genome sequencing to assess evolution of the epidemic (*13*).

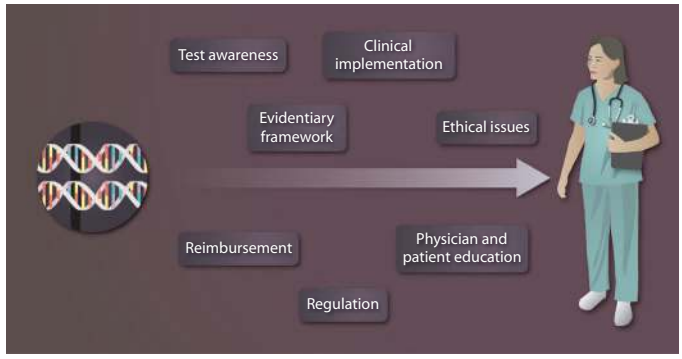

Fig. 3. Challenges facing genomic medicine. Shown are the obstacles on the path from genome discovery to clinical medicine. These obstacles include test awareness (diffusion of innovation), building the evidentiary framework needed to support the clinical validity and utility of genomic tests, implementation of genomic medicine into the clinical workflow, ethical issues surrounding genomic testing, regulatory and reimbursement hurdles, and the education of health care workers and patients alike.

CHALLENGES AND OPPORTUNITIES FOR GENOMICS IN MEDICINE

In the past decade, applications of genome research have been pursued across the spectrum of disease management, from risk assessment through diagnosis, prognosis, and treatment. Several themes in diagnosis and treatment are emerging (Fig. 2). First, as the knowledge of the genomic underpinnings of disease increases, the definition of self is likewise expanding. This self includes not just the germline human genome inherited from our parents but also somatic changes in the genomes of tumors, the genomes of commensal microbes that regularly inhabit our body, and the genomes of pathogenic organisms. Second, the influence of genomics on medicine is moving the diagnosis of diseases toward the earliest possible point in the course of disease, before clinical manifestation. Third, genomic testing is occurring earlier in the life of a human, moving from adulthood to childhood, the neonatal period, and even prenatally. Finally, pharmacogenomics is providing a potential means of improving response to therapies, enhancing safety, optimizing dosing, and tailoring treatment to the molecular underpinnings of disease. Notwithstanding this progress, significant barriers are impeding the rapid translation of genomic discoveries into medical practice.

Whereas research continues on the development, validation, and utility of genome-based biomarkers, attention is now appropriately shifting to addressing the roadblocks in translational genomic medicine, from discovery to clinical implementation (*93*). Here, we highlight some of the most pressing challenges (Fig. 3) along with innovative solutions. What is becoming clear as the field progresses is that integration of genomic medicine into practice requires changes in the infrastructure, processes, and culture along the entire path from discovery to health care delivery.

Evidentiary framework

Building the evidentiary framework needed to convince the FDA to approve genomic tests, insurance companies to cover them, and physicians to use them is perhaps the biggest challenge facing the field of genomic medicine. In this area, genomic medicine may benefit from

partnering with public health agencies, which have vast experience in epidemiology and surveillance. The Office of Public Health Genomics at the U.S. Centers for Disease Control and Prevention has developed a framework for evaluating emerging genetic tests. Their ACCE model encompasses four areas: analytic validity (how accurately and reliably the test measures the genotype of interest), clinical validity (how consistently and accurately the test detects or predicts the intermediate or final outcomes of interest), clinical utility (how likely the test is to significantly improve patient outcomes), and ethical, legal, and social implications that may arise in the context of using the test (*94*). Analytic validity is usually in the purview of the testing laboratory, which undertakes a relatively straightforward process to ensure accurate detection and reporting of the assay results. The bigger challenge is establishing clinical validity and utility, a process that requires data curation from the primary scientific literature and, ultimately, carrying out expensive and time-consuming prospective randomized clinical trials.

The financial burden on a diagnostic developer to conduct randomized clinical trials is substantial. As a result, a number of public-private consortia of stakeholders have emerged to pool resources and validate genomic biomarkers. The Biomarker Consortium (http://biomarkersconsortium.org) is one such example where government and pharmaceutical companies are collaborating on the discovery and qualification of new biomarkers. The Consortium can leverage clinical trial data from multiple pharmaceutical companies, which, when pooled, can markedly increase statistical power and, when coupled with analytical and scientific expertise from academia, government, and the public sector partners, can accelerate and reduce the cost of clinical validation.

In the case of rare diseases, which are the focus of clinical sequencing, or rare outcomes, which are the focus of pharmacogenomic tests for therapeutic toxicities, enrolling adequate numbers of subjects in a randomized clinical trial may not be possible. Moreover, randomized clinical trials do not always represent real-world situations but rather exemplify an ideal circumstance. To address these concerns, some have proposed the use of a pragmatic clinical trial design instead (*95*, *96*). In contrast to randomized clinical trials, with their strict patient eligibility criteria, narrow protocol-driven therapies, and prescribed outcomes, pragmatic clinical trials are conducted in the real-world medical setting, under best-practice conditions with diverse and comorbid patient populations. Although less rigorous in design than randomized clinical trials, the pragmatic clinical trial design could provide an early indication of the value of pharmacogenomic testing. Comparative effectiveness research is a similarly pragmatic approach that uses systematic reviews of existing studies, evidence-quality appraisal, and health outcomes research in real-world practice settings to assess clinical utility. Rapid learning healthcare models are being used for comparative effectiveness research, whereby diverse and interoperable patient clinical and outcomes data are made available, ideally in a robust and real-time fashion, to potentially support clinical practice while simultaneously supporting comparative effectiveness research (*97*). Coupled with biobanking of patient specimens, the clinical utility of genomic tests can be evaluated in an efficient and cost-effective manner (*98*).

Another consideration is that clinical utility conceived only as improved morbidity and mortality fails to appreciate personal utility for the patient, such as the financial and psychological benefits of resolution of an unknown diagnosis, changes in life-style leading to overall improvements in health, or even family planning, all of which are influenced by knowledge of the genetic susceptibility of disease (*99*–*102*). Some groups charged with evaluating genomic tests already recognize that incorporating the concept of personal utility into assessments of clinical utility will more accurately capture the value of these tests (*101*). Through creative partnerships and study designs and a new appreciation of personal utility, the evidence base for genomic medicine tests will expand and, in doing so, facilitate approval, coverage, and adoption by the health care community.

Diffusion of innovation in genomics and medicine

The challenge of diffusion of innovation in health care is not unique to genomic medicine, but the classical venues for disseminating information to health care providers, such as grand rounds and conferences, may be insufficient for capturing the breadth and depth of genomic medicine. Passive approaches, including reading the primary scientific and medical literature, can be time-consuming and overwhelming. Consequently, several efforts are under way to track and make accessible the latest available information on genomic tests (Table 2). For drugs on the market, recommendations for genomic testing can be found in their labels and in a database of drug-test pairs, currently numbering more than 100, maintained by the FDA (*103*). The Pharmacogenomics Knowledge Base (PharmGKB) is another online resource that includes information on 186 potentially clinically actionable gene-drug associations and genotype-phenotype relationships (*104*). Much of the information is manually curated from the published literature and is used to write evidence summaries and pharmacogenomic-based drug dosing guidelines. Another resource is GeneTests (http://www.ncbi.nlm.nih.gov/sites/GeneTests), a site focused on Mendelian disorders that includes a directory of genetic testing laboratories and genetic and prenatal diagnosis clinics as well as expert-authored peer-reviewed disease descriptions in a standard format (GeneReviews). GeneTests is slated to be phased out in 2013 and replaced with the National Institutes of Health's (NIH) Genetic Testing Registry, a repository for comprehensive genetic test information that is voluntarily submitted by test providers (*105*). Currently, the site lists 2793 clinical tests, including pharmacogenetic and other types of tests that are not in GeneTests. Perhaps the most comprehensive list of non-Mendelian genomic tests can be found in a series of Technology Assessment Reports generated by the Tufts Medical Center Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality. Through horizon scanning of the scientific literature, news, laboratory and commercial Web sites, databases, and other sources, researchers at Tufts University have populated a database, Gene Test Tracker, with available clinical genetic tests relevant to the Medicare population. The current reports cite 154 cancer tests (*106*) and 127 noncancer genetic tests (*107*) in development.

Besides databases for tracking available tests, there is a need for curation, evaluation, and synthesis of evidence from published research supporting clinical validity and utility of tests to guide clinicians. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) (http://www.egappreviews.org/recommendations/index.htm), a group formed in 2004 by the Office of Public Health Genomics (*108*), synthesizes scientific evidence and makes recommendations on appropriate use of genetic tests in clinical practice. In 2009, PharmGKB and the NIH's Pharmacogenomics Research Network initiated a similar effort, the Clinical Pharmacogenetics Implementation Consortium (CPIC) (http://www.pharmgkb.org/page/cpicGeneDrugPairs) (*109*). CPIC provides guidelines to help clinicians understand how available genetic test results

Table 2. Genomic medicine's address book. Shown are sites that curate available genomic tests and the evidence to support their use.

Web site	URL	Description
CPIC	http://www.pharmgkb.org/page/cpic	Provides freely available, peer-reviewed, updatable, and detailed gene/drug clinical practice guidelines; 6 currently published, 8 under way
EGAPP	http://www.egappreviews.org/	Synthesizes scientific evidence and makes recommendations on appropriate use of genetic tests in clinical practice; 8 evidence reports and 6 recommendations currently available
Evidence aggregator	http://www.hugenavigator.net/GAPPKB/evidencerStartPage.do	Search engine for evidence reports, systematic reviews, recommendations, or guidelines in genetic tests and genomic applications
FDA biomarkers	http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm	List of pharmacogenomic biomarkers on drug labels (link to drug labels provided); currently includes >100 biomarker-drug pairs
GAPP Finder	http://www.hugenavigator.net/GAPPKB/topicStartPage.do	A continuously updated, searchable database of genetic tests in transition to practice; currently includes 519 tests
GeneTests	http://www.ncbi.nlm.nih.gov/sites/GeneTests/	Information on genetic tests, mostly for rare Mendelian disorders. Site includes directory of testing laboratories, genetic and prenatal diagnosis clinics, and expert-authored peer-reviewed disease descriptions (GeneReviews); currently includes >2900 disease entries; due to be phased out in 2013
Genetic testing registry	http://www.ncbi.nlm.nih.gov/gtr/	Central location for voluntary submission of genetic test information by providers; includes information on test methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials; currently includes >1200 fully registered tests for >500 conditions
PharmGKB	http://www.pharmgkb.org	Information on potentially clinically actionable gene-drug associations and genotype-phenotype relationships; currently lists 186 well-known pharmacogenomic associations and provides 46 summaries for very important genes
PLoS currents: evidence on genomic tests	http://currents.plos.org/genomictests/	Online, open-access journal publishing evidence reviews and recommendations on genomic tests; currently has 23 genomic test reviews

should be used to optimize drug therapy. Currently, CPIC has published recommendations for six gene-drug pairs, with eight more under way. GAPPKB (http://www.hugenavigator.net/GAPPKB/home.do), an integrated, searchable knowledge base, is also attempting to fill this gap. This online resource developed by the Office of Public Health Genomics features the GAPP Finder, a continuously updated, searchable database of genetic tests in transition to practice; Evidence Aggregator, an application that facilitates searching for evidence reports, systematic reviews, recommendations, or guidelines in genetic tests and genomic applications; and PLoS Currents: Evidence on Genomic Tests, an online, open-access journal publishing evidence reviews and recommendations on genomic tests. These early attempts at supporting diffusion of innovation are a laudable first step, but a more sustainable means of curating data on available tests, annotating the scientific literature, and gathering evidence to support genomic tests in an efficient, dynamic, and timely manner needs to be developed.

Clinical implementation

In order for genomic medicine to be practiced, it must be woven into current systems of healthcare delivery, with due consideration not only to the providers of healthcare but also to the organizations in which they practice as well. Implementation scientists have outlined various aspects that need to be considered in order for genomic medicine to take hold in the clinical setting (*110*). Beyond the scientific soundness of the genomic test, measured by a strong evidentiary base and regard for potential benefits and harms, is consideration of how the new test will integrate into the clinical workflow. Consideration should be given to aspects such as access to a laboratory certified by the Clinical Laboratory Improvement Amendments (CLIA) of 1988, methods for sample preparation and transport, test ordering, receipt, and delivery of results. Although these features are not unique to genomic testing, their implementation is complicated by issues of privacy, complex interpretation of results, and the need to involve third parties for counseling in some cases. These facets may require the development of new systems to accommodate genomic tests (*111*). For example, surgical and interventional radiology services are accustomed to fixing tissues in formalin to preserve them for analysis at a later date, but NGS works best on fresh tissues. Either adapting NGS technology to work within the constraints of current tissue handling procedures or modifying those procedures to allow collection of fresh or fresh-frozen tissues may be necessary (*112*).

A robust means of integrating genomic data into electronic health records will be required, with consideration of not only data storage formats and privacy issues but also appropriate decision support tools for prompting their use at the point of care and delivering results in an easily interpretable format (*113*–*115*). To meet these needs, NGS companies like Knome (http://www.knome.com) are developing their own plug-and-play bioinformatic support tools, and commercial vendors of electronic health records have begun to address genomic-related applications as well (*113*). Some patients may opt to self-manage their own genomic data in a personal health record such as Microsoft Health Vault (http://www.microsoft.com/en-us/healthvault) or Dossia

(http://www.dossia.org) as a safeguard. Currently, there are several examples of decision support tools, such as Warfarin Dosing (http://www.WarfarinDosing.org), but they are typically standalone tools and not part of routine clinical workflow. To maximize their effectiveness, such tools should be integrated into electronic health records. Tapping into the collective knowledge and experience of various institutions working in this space would greatly facilitate this effort. Ultimately, a national, standardized technical architecture for integrating clinical decision support into electronic health records will be required. Notable efforts in this space include those of Health Level 7 (http://www.hl7.org), an organization that provides interoperability standards for the exchange, integration, sharing, and retrieval of electronic health information. Through their Clinical Genomics Workgroup, this organization has developed a standards guide for genetic testing that includes document templates to support integration of genetic testing into electronic health records (*116*). Appropriate clinical decision support, provided in the context of the electronic health record, will greatly facilitate the diffusion and uptake of genomic medicine.

Regulation of genomic tests

Regulation of genomic tests is both a public health issue and, ultimately, an economic one. Physicians and patients alike look to government regulators to assure them that the tests have been carefully scrutinized for their safety, efficacy, and intrinsic value. Currently, two federal organizations are in charge of regulating genetic tests (*117*). A small percentage of genetic tests are sold as diagnostic devices, meaning that a company makes and sells genetic test kits to a laboratory for testing, and these are regulated by the FDA's Office of In Vitro Diagnostics. Before marketing, the analytical validity of the device must be assessed, but in cases where clinical performance has not been well established, the clinical validity is examined as well. The specific degree of regulation of medical devices is currently tailored to their level of risk: class I (low risk, few regulatory controls), class II (moderate risk), and class III (high risk, more controls, including submission of a premarket approval application) (*117*). Many genomic tests will fall into class II, as is the case with genetic tests for drug-metabolizing enzymes (*118*). Some genomic tests will fall into class III, for example, those that alter a therapeutic decision in such a way as to expose individuals to potentially harmful treatments, such as radiation therapy in cancer. Recent guidance from the FDA clarifies the principal factors it considers when making benefit-risk determinations on medical devices (*119*).

Most genetic tests today are developed and offered by individual laboratories as laboratory-developed tests, and these laboratories are overseen by the Centers for Medicare and Medicaid Services (CMS). CMS is primarily concerned with monitoring the laboratory's compliance with CLIA regulations in their testing procedures. For years, the FDA has claimed enforcement discretion and opted not to regulate laboratory-developed tests unless they were deemed "high risk," as in the case of IVDMIAs (*76*). However, the selective approach to regulate only a subset of high-risk laboratory-developed tests has led to more confusion and created an uneven playing field. Moreover, the rise of direct-to-consumer genetic testing companies, those that bypass physicians and market their services directly to patients outside the medical setting, has brought regulatory oversight of genomic tests in general to the forefront (*120*). On the basis of a series of recommendations by the U.S. Department of Health and Human Services Secretary's Advisory Committee on Genomics, Health, and Society to enhance oversight (*121*), the FDA has responded with a 2010 notice stating that they may actively regulate not just high-risk tests but all laboratory-developed tests (*122*). Regulation of genomic tests is a moving target that needs to strike a balance between commercial interests and patient safety to move genomic medicine forward.

Coverage and reimbursement

Although FDA approval of a genomic medicine test may improve the likelihood of coverage by insurance companies, it is no guarantee. Whether an insurance plan covers genetic testing depends on several factors, including consumer demand, opinions of professional organizations, integration into clinical guidelines, and, most importantly, the strength of evidence supporting a test's analytical and clinical validity and clinical utility (*123*). Private insurance plans all make their own decisions regarding whether to cover and how much to reimburse for a genomic test, and it can vary on a case-by-case basis within those plans. Nonetheless, private insurers often mimic the coverage decisions of Medicare, as the largest provider of health insurance in the United States. Medicare decisions are made by CMS, which has a policy of reimbursing tests that are reasonable and necessary for diagnosis or treatment of an illness or injury. However, CMS does not typically reimburse screening tests, including genetic predisposition tests, except in the presence of signs and symptoms of disease. CMS's Medical Evidence Development and Coverage Advisory Committee met in 2009 to discuss what types of evidence will be needed to evaluate screening genetic tests for Medicare coverage (*124*). This information should help guide future development of genomic tests to improve their likelihood of coverage.

In a further sign that the field is moving forward, the American Medical Association issued a new coding system for molecular diagnostics, and the CMS has been deliberating on how to reimburse these tests (*125*). One of the key challenges will be obtaining reimbursement not just for the pathology laboratories that are running the tests but also for the physicians or other health care workers who are interpreting the tests. Coverage and reimbursement of genomic tests is evolving, but in the current system of healthcare delivery, it remains an essential component that needs to be addressed to see widespread uptake of genomic medicine.

Ethical, legal, and social issues

Many of the ethical, legal, and social issues related to genomic medicine—such as patient privacy, selective termination of pregnancies based on genetic information, and patentability of DNA—have existed since the arrival of genetic testing. In a current landmark case sparked by controversy over the *BRCA1* gene patent held by Myriad Genetics—*Association for Molecular Pathology, et al. v. U.S. Patent and Trademark Office, et al.*—the U.S. Supreme Court is hearing arguments on the patentability of genes (*126*). The ruling will have implications for diagnostic use of gene patents, affecting developers of diagnostics and patients alike. Privacy is another issue that has been reignited by the introduction of NGS and fueled by an atmosphere of collaborative, open-access public data sharing. Studies of publicly available sequence data have shown that patients in research studies can be identified by their genome sequences (*127*, *128*). These findings demonstrate the potential for sequence data to expose patient identities, with significant implications for not only the individual but also their family members and possibly the larger community to which they belong. The 2008 Genetic Information Nondiscrimination Act is a U.S. federal law that bars insurers and employers from discriminating on the basis

of genetic information, but it does not pertain to long-term disability or life insurance, nor does it protect against stigmatization. The application of NGS to noninvasive prenatal testing has also rekindled an old concern over the misuse of genetic information to perform selective abortion, already an ethically and politically contentious issue. Fear that decisions will be made on the basis of trivial genetic traits has reopened the debate about which health conditions, if any, are sufficient grounds to justify abortion (*129*).

The ability to uncover all genetic variants in a subject through NGS also raises a new dilemma: whether to disclose to patients potentially clinically meaningful variants unrelated to the primary indication for sequencing, so-called secondary or incidental findings (*128*, *130*). On average, every human has several hundred coding region variants in their genomes, most of which have unknown health consequences (*6*). Who decides which of the discovered mutations are clinically relevant and under what circumstances the incidental findings of NGS, of either known or unknown health significance, should be shared with patients are hotly debated topics. The American College of Medical Genetics advocates for clear policies related to return of results, stating that patients should be informed of those policies and understand what types of information might be reported back to them and under what circumstances, as well as recommending that patients should be able to opt out of receiving certain findings (*131*). In their recently published position statement, the American College of Medical Genetics recommends that laboratories conducting exome and genome sequencing for clinical use should notify physicians about their patients' status for a number of specific conditions, genes, and variants that are found during the sequencing (*132*). This position has been controversial because it is seen to be at odds with patient autonomy and the rights of children to not learn about genetic predisposition to adult-onset conditions. This has led the American College of Medical Genetics to release a statement clarifying their position (*133*).

The limited understanding of the health implications of genetic variation uncovered through NGS is concerning. In 2011, the National Human Genome Research Institute sponsored a workshop, ClinAction, to devise a plan for systematically evaluating and cataloguing genetic variants based on their clinical actionability (*134*). The experts in attendance proposed storing data on actionable variants in a new database, ClinVar (http://www.ncbi.nlm.nih.gov/clinvar), which could be integrated into the clinical workflow. Initially, the database will be populated with existing variants catalogued in the Online Mendelian Inheritance in Man database (http://www.omim.org), GeneReviews (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review), Locus-Specific Mutation Databases (http://www.hgvs.org/dblist/glsdb.html), and other sources, but will grow as new discoveries are made. An important aspect of this effort is the need to guard against false-positive results that can occur in NGS studies based on single patients or families, and for which very strict peer review of the scientific evidence linking the genetic variant to disease is warranted. Fortunately, discourse on incidental genetic findings as well as other ethical issues is occurring in parallel with development of genomic medicine as the research community strives to balance innovation with responsible use of new technologies.

Education

There is a growing sentiment that uptake of genomic medicine is slow because health care providers lack adequate training in genomics. One study found that describing a test as genetic (versus nongenetic) significantly decreased a physician's likelihood of offering the test (*135*). Primary healthcare providers will likely assume prominent roles at the front lines of genomic medicine, taking responsibility for administering new tests and fielding questions from informed patients. Hence, they will not only need to be armed with practical information on what tests are available, when and how to use them, where to get them done, and what to tell patients, but also require a conceptual foundation on which to build their capacity to evaluate and deliver genomics in the course of clinical care. Although most physicians have heard of pharmacogenomics (*136*), few are aware of direct-to-consumer genetic testing (*137*), and with the rapid pace of discovery, staying on top of the latest available genomic medicine tools will be a daunting task. Research has shown that few primary care providers feel comfortable ordering genomic tests or explaining test results to patients (*136*, *137*), and most feel an urgent need for genetics education (*138*).

In their report on genetics education, the U.S. Department of Health and Human Services Secretary's Advisory Committee on Genomics, Health, and Society highlighted factors that contribute to the limited genetics education of healthcare professionals, including issues such as a crowded curricula, lack of knowledgeable faculty, lack of evidence-based guidelines in genetics, and misconceptions about the nature of genomic medicine (*139*). The committee recommended modifications in medical, dental, nursing, public health, and pharmacy school curricula and in medical residency training programs to ensure that healthcare professionals entering the workforce are well trained in genetics. These recommendations prompted the National Coalition for Health Professional Education in Genetics to develop specific core competencies for all health care professionals on knowledge, skills, and attitudes needed to effectively deliver genomic medicine (*140*).

But still unresolved are the best methods to educate health care providers. In the last few years, several university medical schools have made significant efforts to fill the genomics education gap (*141*–*144*). These efforts include targeting curriculum to medical students and residents in training and continuing medical education for practicing professionals. There is a push to introduce topics related to genomic medicine even earlier, during undergraduate training. However, improving overall genomics literacy of health care providers is only one piece of the puzzle, and keeping pace with this rapidly evolving field will be a continuous challenge.

Enhanced genomic education not only is key for health care providers but also extends to all professions that genomic medicine touches upon. Policy-makers, regulators, lawyers, investors, insurance underwriters, and others will need some understanding of genomics to move genomic medicine forward. It remains unclear how these professionals will receive this information. Moreover, acceptance of genomics ultimately may require a level of comfort on the part of the patient, who may be concerned about privacy and discrimination or confused about the implications of a particular genetic test result. This may be especially problematic for patients obtaining genomic data through direct-to-consumer test providers. Studies find that more than one-third of U.S. adults have limited health literacy (*145*), which in turn affects understanding of print and oral communications about genetic and genomic information (*146*). Historically, genetic counselors have been responsible for putting genetic information into context for patients undergoing genetic testing, but these situations have mainly involved Mendelian traits with clear inheritance and strong effects and have occurred in the domain of specialty genetics clinics. As genomics spreads from specialty clinics to more mainstream medicine where primary care physicians will be utilizing genomic information

for clinical decision-making, the demand for genetic counselors may far outstrip the supply, making this model impractical. Alternative solutions, including additional training, and perhaps certification, of primary health care providers in the delivery of genomic medicine will need to be considered. In addition, improvement in the formal primary and secondary education of consumers in the areas of scientific and health literacy will enhance informed decision-making (*93*).

FUTURE EXPECTATIONS

The late 1990s marked what many consider to be the dawn of the era of personalized medicine, when the full human genome was being revealed for the first time and scientists were beginning to explore the many ways that this information could be used to improve medicine (*147*). Today, genome research has delivered promising new tools for disease management, and early signs of uptake at academic medical centers are encouraging. To be sure, the pace of implementation has been slower than anticipated, and genomic medicine is far from mainstream. Nonetheless, the challenges that prevent more widespread uptake are not intractable but will require a concerted effort by the many stakeholders in the field to overcome.

Moving forward, technological advances will continue to drive discovery. New applications of NGS are on the horizon, including profiling of immune cell repertoires (*5*) for monitoring hematological malignancies (*148*, *149*) and responses to vaccines (*150*), and detecting solid transplant rejection (*151*), just to name a few. Third-generation sequencing platforms are expected to provide longer read lengths, chromosome phasing, and reduced time and cost, increasing the accuracy, capacity, and turnaround time for genome sequencing (*152*). Not only will future research efforts lead to new markers and tools to predict and manage disease at an increasing rate, but we also may see fundamental shifts in how we define disease, how medicine is delivered to patients, and how consumers manage their own health and affect change.

Creative partnerships and a rise in consumer-driven genomic research

The pace of genomic biomarker discovery will continue to accelerate through creative research and funding partnerships. Large disease-centered consortia are already bringing together investigators to collaborate and pool data and resources. For example, the International Cancer Genome Consortium (*153*) involves 51 project teams contributing genomic data from 24,000 tumors across a wide spectrum of cancers (http://icgc.org). The open-access movement will continue to promote data sharing through portals such as Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo) and dbGaP (http://www.ncbi.nlm.nih.gov/gap), where any qualified investigator can generate hypotheses and analyze data. Educated patients are also becoming a driving force behind personalized medicine. The movement toward consumer-driven health care has empowered patients, leading them to seek information on medical conditions through the Internet, track their own health history through personal health records, and obtain genomic data through direct-to-consumer genetic testing companies. The downside of this trend is that, without a medical professional to help with the interpretation of the information, patients may misinterpret their genetic information, which could lead to unnecessary stress or misinformed health decisions. Patients are now networked through social media, sharing information on health conditions through sites like PatientsLikeMe (http://www.patientslikeme.com) and, in some cases, bypassing the medical establishment altogether. Crowd-sourcing, crowd-funding, and participant-driven research are also on the rise. The direct-to-consumer genetics company 23andMe has proven the feasibility of web-based collection of self-reported data from an engaged cohort of research participants that can be used for genomic research in some cases (*154*). Although these efforts are not without their caveats, including the potential for bias and confounding leading to spurious results (*155*, *156*), and will not replace carefully designed epidemiological studies, they represent an innovative approach to overcoming some of the financial and logistical constraints inherent in genomic research. Another example of this trend is the newly launched American Gut project (http://humanfoodproject.com/american-gut), an open-source, community-driven effort to characterize the microbial diversity of the American public where study subjects are recruited online and not only participate in research but also help to fund it.

New taxonomy for disease

In the coming years, we will likely see a fundamental shift in how disease is classified. Currently, diseases are classified on the basis of subjective clinical signs and symptoms and, in some cases, objective laboratory or image-based tests. Absent from this framework in most cases is a measure of the perturbed molecular pathways that characterize the disease. Genomics is poised to deliver molecular-level definitions of the physiological processes underlying diseases, suggesting treatments targeted at the molecular lesions instead of the symptoms. Nowhere is this more evident than in cancer, where subclassification of disease is having a tangible effect on treatment and where tissue of origin is secondary to the molecular profile of the tumor. The current disease classification system used in the health care industry as a basis for diagnosis and reimbursement is the International Statistical Classification of Diseases and Related Health Problems (ICD), currently in its 10th revision (ICD-10) (*157*). The ICD-10 for oncology already incorporates genomic factors to distinguish subtypes of cancer (*158*–*160*). ICD-11, the next revision, due to be published in 2015, promises to expand this theme. Momentum on creating a new disease taxonomy is growing, as evidenced by an extensive report on development of precision medicine by the National Research Council of the U.S. National Academies of Science (*161*) and the prioritization of precision and personalized medicine this year by the World Economic Forum (*162*).

New methods for delivering genomic medicine preemptively

Because the cost of sequencing continues to decline and the analytical issues abate, it is conceivable that individuals will have their genome sequenced at some point in their lives, perhaps even at birth. Health systems will likely incorporate all or part of one's genomic information into their electronic medical record. Thus, critical information on pharmacogenetic markers of toxicity or drug response, for example, would be available preemptively, before prescribing a drug. This model is already being piloted in the NIH's eMERGE program (*163*) at Vanderbilt University as part of their PREDICT initiative (*164*) and at other institutions as well (*165*). Compared to current testing practices, such an approach could provide a more cost-effective means to capture and treat rare, preventable genetic diseases missed by the current health care system, aid in future family planning, and improve safety and efficacy of therapies.

Point-of-care diagnostics and digital medicine

New ways of delivering personalized medicine are being developed for use at the bedside and beyond. Point-of-care diagnostic tests will facilitate rapid diagnosis at the patient's bedside, physicians' offices, emergency rooms, and at home (*166*). We will see a rise in the use of digital medicine, where patients monitor their own vital statistics at home through sensors and handheld devices and send data directly to their doctor (*167*). One day, this monitoring may include dynamic measures of the genome including longitudinal, integrated personal "omics" profiles (*168*) or gene expression changes indicative of exposure to infectious agents (*169*).

Rise in third-party genomic information brokers

Genome interpretive services will emerge to assist clinicians in understanding the meaning and actionability of genome information, much the same way as radiologists assist in the interpretation of imaging. This nascent field currently includes startup companies like Knome (http://www.knome.com), Personalis (http://www.personalis.com), Omicia (http://www.omicia.com), Genomatix (http://www.genomatix.de), Cypher Genomics (http://cyphergenomics.com), Silicon Valley Biosystems (http://www.svbio.com), and GenomeQuest (http://www.genomequest.com), who are offering software, computer infrastructure, and services required to process, analyze, and store patient sequence data and, in some cases, even produce tailored diagnostic reports.

CONCLUSION

Genomic medicine—only an aspiration 10 years ago— is beginning to emerge across the entire clinical continuum from risk assessment in healthy individuals to genome-guided treatment of complex diseases in patients. Technology continues to propel the field forward, but translating discovery into routine use is complex, requiring changes in the fundamental processes of regulation, reimbursement, and clinical practice. Progress is tempered by consideration of ethical issues and the need to fill the education gap that exists for health care providers and consumers alike, which makes it difficult to keep pace with advances in the field. External forces from social networking to digital and information technologies are enabling consumers to take health matters into their own hands, generating momentum like never before. Today, we are on a path toward implementation of genomic medicine, but that path is long, mired with obstacles, and potentially perilous. Moreover, it remains to be seen whether genomic medicine will actually improve health, when efforts to implement simpler clinical and preventive strategies have failed. Nonetheless, the movement toward improving disease diagnosis and treatment with genomics is unlikely to halt and there is reason to be optimistic. How will we know when we have arrived? When we stop talking about genomic medicine, and refer to it simply as medicine.

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