Genomic and Personalized Medicine: Foundations and Applications

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Genomic and personalized medicine: foundations and applications

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The last decade has witnessed a steady embrace of genomic and personalized medicine by senior government officials, industry leadership, health care providers, and the public. Genomic medicine, which is the use of information from genomes and their derivatives (RNA, proteins, and metabolites) to guide medical decision making—is a key component of personalized medicine, which is a rapidly advancing field of health care that is informed by each person's unique clinical, genetic, genomic, and environmental information. As medicine begins to embrace genomic tools that enable more precise prediction and treatment disease, which include "whole genome" interrogation of sequence variation, transcription, proteins, and metabolites, the fundamentals of genomic and personalized medicine will require the development, standardization, and integration of several important tools into health systems and clinical workflows. These tools include health risk assessment, family health history, and clinical decision support for complex risk and predictive information. Together with genomic information, these tools will enable a paradigm shift to a comprehensive approach that will identify individual risks and guide clinical management and decision making, all of which form the basis for a more informed and effective approach to patient care. DNA-based risk assessment for common complex disease, molecular signatures for cancer diagnosis and prognosis, and genome-guided therapy and dose selection are just among the few important examples for which genome information has already enabled personalized health care along the continuum from health to disease. In addition, information from individual genomes, which is a fast-moving area of technological development, is spawning a social and information revolution among consumers that will undoubtedly affect health care decision making. Although these and other scientific findings are making their way from the genome to the clinic, the full application of genomic and personalized medicine in health care will require dramatic changes in regulatory and reimbursement policies as well as legislative protections for privacy for system-wide adoption. Thus, there are challenges from both a scientific and a policy perspective to personalized health care; however, they will be confronted and solved with the certainty that the science behind genomic medicine is sound and the practice of medicine that it informs is evidence based. (Translational Research 2009;154:277–287)

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Abbreviations: AHIC = American Health Information Community; CDS = clinical decision support; CMS = Centers for Medicare and Medicaid Services; FDA = U.S. Food and Drug Administration; FHH = family health history; HIT = health information technology; HRA = health risk assessment; PBMC = peripheral blood mononuclear cell; SNP = single-nucleotide polymorphism; VKORC1 = vitamin K epoxide reductase complex protein 1

> Over the past decade, we have unlocked many of the mysteries about DNA and RNA. …This knowledge isn't just sitting in books on the shelf nor is it confined to the workbenches of laboratories. We have used these research findings to pinpoint the causes of many diseases. … Moreover, scientists have translated this genetic knowledge into several treatments and therapies prompting a bridge between the laboratory bench and the patient's bedside.
>
> *President Barack Obama*
> *On the Genomics and Personalized Medicine Act (S.976), March 23, 2007*

> …We are in a new era of the life sciences, and the truth of that statement can be seen in fields from medical imaging, to new biologic drugs, and even to the use of DNA technology to improve our environment and reduce greenhouse gasses. But in no area of research is the promise greater than in the field of personalized medicine.
>
> *Senator Edward M. Kennedy*
> *On the Senate's Consideration of the Genetic Information Nondiscrimination Act, April 24, 2008*

More than 10 years ago, reporters for *The Wall Street Journal* wrote an article titled "New Era of Personalized Medicine—Targeting Drugs for Each Unique Genetic Profile,"[1] which set high expectations for a new way of practicing medicine predicated on the characteristics of the individual. In 2007, then-Senator Obama put forth legislation in the Genomic and Personalized Medicine Act of 2007[2] that aimed to create the necessary resources and integrate government stakeholders to advance this new field of medicine. The last decade has experienced a steady embrace of personalized medicine by senior government officials, industry leadership, health care providers, and the public. It is now appropriate to reflect on and summarize the achievements and advances that have been made to reach the lofty goals inherent in the term "personalized medicine."[3]

Arguably, the concept of personalized medicine has been anticipated for decades. Sir William Osler (1849–1919) recognized that "variability is the law of life, and as no two faces are the same, no two bodies are alike, and no two individuals react alike, and behave alike under the abnormal conditions we know as disease." The elucidation of "factors of risk" from the Framingham Heart Study in the 1960s was among the first population-based efforts to define strata within a population composed of individuals at a higher risk for developing coronary artery disease. What has changed since then—dramatically—is that we now have, as a result of the Human Genome Project, a new set of tools that can be used to understand the complexity of the underlying biology of disease and its variability. These tools enable us to refine risk prediction and predict the response to therapies with greater precision than has ever been possible. Genomic and personalized medicine allows health care providers as well as patients to use predictive tools in what is emerging as a new model for health care, one that is based on proactive and preventive health planning, as opposed to the traditional model of reactive, episodic health care geared toward acute crisis intervention once disease is already manifest and largely irreversible.

WHAT IS GENOMIC MEDICINE?

Simply defined, genomic medicine is the use of information from genomes (from humans and other organisms) and their derivatives (RNA, proteins, and metabolites) to guide medical decision making. The prospect of examining a person's entire genome (or at least a large fraction of it) to make individualized risk predictions and treatment decisions is now possible. Many patterns of gene expression across the entire genome are also now readily assayed. Thus, health and disease states can now be characterized by their molecular fingerprints to develop meaningful stratifers for patient populations and to elucidate mechanistic pathways based on genome-wide data.

WHAT IS PERSONALIZED MEDICINE?

Personalized medicine is a broad and rapidly advancing field of health care that is informed by each person's unique clinical, genetic, genomic, and environmental information. Health care that embraces personalized medicine is an integrated, coordinated, evidence-based approach to individualizing patient care across the continuum (from health to disease). Personalized medicine depends on using multidisciplinary health care teams

to promote health and wellness, patient education and satisfaction, and customized disease prevention, detection, and treatment. Personalized medicine uses genomic medicine to take advantage of a molecular understanding of disease to optimize preventive health care strategies and drug therapies while people are still well or at the earliest stages of disease. The overarching goal of personalized medicine is to optimize medical care and outcomes for each individual, to include treatments, medication types and dosages, and/or prevention strategies may differ from person to person—resulting in an unprecedented customization of patient care.

WHAT ARE THE TOOLS THAT ENABLE RISK ASSESSMENT AND PREDICTION?

Health risk assessment (HRA). A fundamental component of personalized medicine is a standard HRA to evaluate an individual's likelihood of developing the most common chronic diseases (or disease events). Evidence-based HRAs coupled with predictive models will facilitate assessment and prioritization of a patient's disease risk. One of the most widely recognized HRAs is the Framingham Coronary Heart Disease Model, which was developed from the Framingham Heart Study that began in 1948.[4] The Gail model and its modified versions are some of the most widely accepted tools for breast cancer risk assessment.[5] Despite the proven value of many risk-assessment tools, they have not been generally embraced as part of the formal patient evaluation because of both the lack of standards for the clinical data required or the algorithms used, as well as the lack of integration into health information technology (HIT) systems.[6] Yet, HRAs should form the basis for prediction and risk stratification that is fundamental to personalized health care. And as novel biologic information and predictive molecular markers are discovered and validated, it is essential that these new markers be iteratively evaluated for their ability to augment the predictive ability of existing clinical models; if so, they should incorporated into the HRA. As personal and electronic health records (EHRs) proliferate and become interoperable, HRAs will also become the standard of care and the starting point for personalized health care.

Family history. Family health history (FHH) is a simple and yet invaluable tool for the delivery of personal health risk information. Reflecting the complex combination of shared genetic, environmental, and lifestyle factors, FHH integrates genetics/genomic risk information into patient care. A robust FHH assessment would help identify persons at higher risk for disease, enabling preemptive and preventive steps, including lifestyle changes, health screenings, testing, and early treatment as appropriate (see Table I[7-11]). As such, FHH holds tremendous potential for improving preventive health care across broad, diverse populations in a personally relevant manner. However, the assessment and integration of FHH information has not been embraced by the health care community and remains a largely untapped resource. Like HRAs, the challenge of incorporating FHH into the publics' health involves the following 3 essential components: (1) accessible, standard collection methods; (2) health care provider access; and (3) clinical guidance for interpretation and use. Currently, the collection may be incomplete, difficult to interpret, and/or vary significantly in content among a patient's health care providers. In addition, providers may have insufficient knowledge and training to interpret FHH accurately for the risk of inherited genetic syndromes and/or common complex conditions.[12]

Recent advances in HIT and standards have set the stage for an opportunity to address these 3 areas and optimize use of FHH for preventive medicine. The American Health Information Community's (AHIC) Family Health History Multi-Stakeholder Workgroup developed a set of standards for the core information for an FHH within an electronic medical record or electronic personal health record.[13,14] The Surgeon General released My Family Health Portrait 2.0, which incorporates the AHIC standards and was designed in an open-source platform intended to enable sharing and interoperability with multiple health information systems.[15] Furthermore, the development of clinical decision support (CDS) tools (*vide infra*) provides a framework to improve FHH use through a familial risk interpretation linked to preventive care guidance. The integration of electronic CDS-supported FHH systems will be a critically important step in the advancement of personalized health care. It is encouraging that an international decision support standard for the provision of CDS has been adopted and disseminated by the Health Level 7 international standards development organization.[16]

Genome information. The completion of the reference human genome sequence has facilitated the discovery and cataloging of variation in that sequence among different individuals (including both healthy individuals and those with various diseases) and among different populations.[17] It has been estimated that some 10–15 million common sequence variants are of sufficient frequency (minor allele frequency at least 5%) in 1 or more populations to be considered polymorphic in humans. In addition, countless rare variants exist, many of which probably are found in only a single or a few individuals and will only be accessible by direct genome sequencing.

In the context of genomic and personalized medicine, a key question is to what extent the genome influences the likelihood of disease onset, determines or signals the natural history of disease, and/or provides clues relevant to the management of disease. A variation in

Table I. Family history-based risks for common conditions

Condition	Relationship	Increased Risk (OR)	Reference(s)
Diabetes, type 2	1st Degree	2.3–2.8	7, 8
Coronary artery disease	1st Degree	3.8	9
Coronary artery disease	2nd Degree	2.2	9
Colon cancer	Parent or sibling	2–2.6	10
Breast cancer	Parent or sibling	1.6–2	10
Lung cancer	Parent or sibling	1.7–2.5	10
Attention deficit/hyperactivity disorder	Child or sibling	2–8	11

Abbreviation: OR, odds ratio.

one's constitutional genome can have several different direct or indirect effects on gene expression, thus contributing to the likelihood of disease.

Having access to the entire human sequence is a necessary but insufficient prerequisite for genomic and personalized medicine. What is equally important is having the technology at hand to visualize individual genomes reliably (as well as their derivatives the transcriptome, proteome, and metabolome [see Table II[17]]) for health and disease status.

Because all these technologies are genome scale and high throughput, patterns of biomarkers (as opposed to measurements of single entities) are becoming more commonplace.[18] The benefit of detecting multiple measures of change is the ability to view the downstream biologic events in aggregate, which yields a more complete picture of the disease potential, progression, or prognosis earlier in the process. The integration of information (both individual genome sequences and relevant biomarkers from the expressed genome) with health system data for individuals will be critical to achieving the goals of genomic and personalized medicine.[19]

Clinical decision support. Despite the potential for genomic information to transform health care, past experience indicates that new genomic interventions, like any new medical intervention, will remain substantially underused for many years unless a robust infrastructure is established for supporting its appropriate use. Clinical research results require an average of 17 years to be routinely implemented in clinical practice,[20] and a landmark 2003 study assessing over 400 quality indicators found that U.S. adults only receive about half of the recommended care.[21] Moreover, genomic interventions may face even greater barriers to clinical adoption compared with more traditional medical interventions, because of such factors as limited clinician familiarity with genomics[22] and the volume and complexity of the underlying data that may need to be considered.

Of the many strategies that have been evaluated for promoting evidence-based care, CDS is a strategy has been found to be particularly effective, which entails providing clinicians, patients, and other health care stakeholders with the pertinent knowledge and/or person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care.[23] More than 90% of clinician-directed CDS interventions evaluated in randomized controlled trials have significantly improved patient care, provided that the CDS was delivered automatically as a part of clinician workflow, was offered at the time and location of decision making, recommended a specific course of action, and used a computer to generate the recommendation.[24]

Table II. The genomic medicine toolbox

Data set ('omic approach)	Technology platform or approach
Human genome sequence (genomics)	SNPs, CNVs (~10–15 million)
Gene expression profiles (transcriptomics)	Microarrays of ~25,000 gene transcripts
Proteome (proteomics)	Protein profiles of specific protein products (~100,000)
Metabolome (metabolomics)	Metabolic profiles (1000 to 10,000 metabolites)

Abbreviation: CNV, copy number variant.

Extended to genomic and personalized medicine, CDS supports the consistent and evidence-based application of genetic and genomic information in health care in many ways. For example, when initiating warfarin therapy using an electronic prescribing system, a clinician could be provided with recommendations on dosing and monitoring that account for the patient's CYP2C9 and VKORC1 genotypes.[25] As another example, to support a clinician in his or her treatment of a patient with breast cancer, an EHR system could consider the gene expression profile of the patient's cancer biopsy and provide an individually tailored prediction of how the patient is likely to respond to various therapeutic options.[26] In championing this vision, former U.S. Department of Health and Human Services Secretary Leavitt identified the enabling of personalized health care through HIT a priority area of his department.[27] Moreover, the Secretary's Advisory Committee on Genetics, Health, and

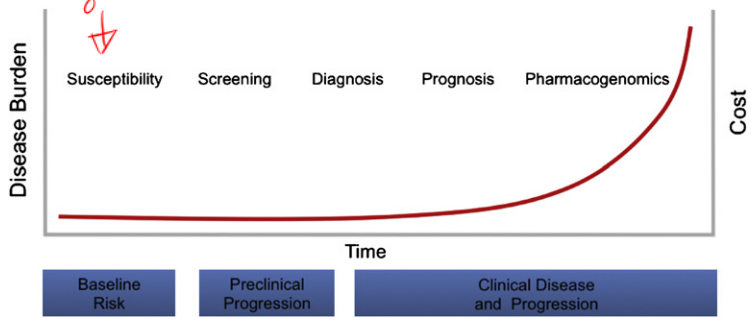

Fig 1. Diagram of the course of a chronic disease over time (red curve), illustrating the opportunities (over time) to use various molecular and clinical tools to refine risk of developing disease as well as screening, diagnosis, prognosis, and therapeutic selection. Adapted from Snyderman.[30] (Color version of the figure is available online.)

Society has identified CDS as an important component of the HIT infrastructure required for the widespread and effective practice of personalized medicine.[27] Critical to this vision of genomic and personalized medicine supported by IT will be a national CDS infrastructure that enables authoritative, centrally curated knowledge on genomic medicine to be consistently leveraged in clinical practices across the nation.

APPLICATIONS OF GENOMICS AND PERSONALIZED MEDICINE

Along the continuum from health to disease (as shown in Fig 1[30]), there are now several important time points at which genomic applications are personalizing health care.[28,29] Disease susceptibility and risk can now be quantified and anticipated during health and even at birth using "stable genomics" or DNA-based assessments that do not change over a person's lifetime. The other 'omics that are dynamic and interact with and respond to environmental stimuli, lifestyles, diets, and pathogens are rapidly improving capabilities to predict and intervene at an individual level. Transcriptional profiles, protein expression patterns, and levels of metabolites combined with dynamic imaging modalities will provide more precise ways to screen individuals who are at high risk for developing a disease for its earliest molecular manifestations while the disease is subclinical. This same information may provide a definitive diagnosis and a molecular classification that foretells prognosis. Similarly, the selection of drugs can be guided both by the patient's underlying genetic makeup as well as by the molecular architecture of the disease in the individual. Given that a disease's evolution from baseline risk often occurs over many years, health care providers must focus on strategic health planning during the most cost-effective times of a disease's life cycle to shift the current paradigm of care from disease treatment to disease prevention.

Disease susceptibility. Genetic linkage studies in families with hereditary breast and ovarian cancer syndromes as well as families with hereditary colon cancer have led to the identification of several important loci that are used for screening, disease risk counseling, and preventive treatment programs.[31-33] Women who carry mutations in either *BRCA1* or *BRCA2* have a high risk for breast and ovarian cancer, and it is now recommended that women in such families have the opportunity to undergo genetic testing to make decisions about surveillance or even surgical approaches to mitigating a high risk of developing breast cancer.[34] Similarly, people in families with a strong history of colon cancer can undergo testing for genes such as *MLH1* and *MSH2* that may identify individuals who have a risk as high as 60% for colon cancer. Early and regular screening colonoscopy in these individuals (as opposed to the recommendation for the general population to begin screening at age 50) may enable the early detection of colon cancer.[33]

Genome-wide association studies during the past 5 years have identified genetic risk factors several common chronic diseases, which include diabetes and heart disease, as well as common cancers.[35] It remains to be observed whether and how these new genetic risk factors will contribute to clinical evaluation of patients for these diseases. Nonetheless, hundreds of new discoveries of genetic factors in common disease have pointed to pathways that, for the most part, we did not anticipate were involved in those conditions. That makes it increasingly likely that these findings will lead to greater insights into the biology and will provide additional therapeutic strategies to approach disease mitigation and possible prevention.

Diagnosis and prognosis. Whole-genome expression data are now being used routinely to identify subtypes of cancer not previously recognized by traditional methods of analysis: profiles and patterns that identify new subclasses of tumors, such as the distinction between acute myeloid leukemia and acute myeloid leukemia,[36] or Burkitt's lymphoma from diffuse B-cell lymphomas,[37] without prior knowledge of the classes. More recently, several genomic signatures that go beyond

disease classification have been discovered and validated that predict prognosis and response to therapy for many solid tumors,[38] and hematologic malignancies.[39]

Last year, for example, oncologists used RNA expression signatures for risk stratification and prognosis in breast cancer for more than 36,000 ''treat'' versus ''no-treat'' decisions.[40] For lung cancer, a similar opportunity now exists to refine prognosis and redirect treatment in early stage disease.[38] Emerging data from other fields of medicine suggest that genomic signatures can stratify disease once it occurs into classes for which genomic data might dictate different therapeutic options. Thus, clear examples now indicate where genomic information is redefining disease phenotypes and refining therapeutic strategies.

Pharmacogenomics. The impact of the genome on our ability to predict drug response is one of the most promising and fertile areas of genomic and personalized medicine. Pharmacogenetics is the study of genetic variation that ultimately gives rise to the variable responses in individuals to any given drug treatment. Pharmacogenomics uses genomic technology to understand the effects of all relevant genes on the behavior of a drug or conversely the effect of a drug on gene expression. Pharmacogenomics, like pharmacogenetics, has rapidly embraced genomic technologies to identify molecular patterns of response, drug disposition, and drug targets, yielding molecular biomarkers of drug response, both of which have great potential to affect the area of medicine positively. In the last decade, a wide range of pharmacogenomic tests have been recognized by the clinical and regulatory communities as having significant potential to alter standard medical practice. Information about genetic testing is now part of the drug label for abacavir, warfarin, clopidogrel, prasugrel, and irinotecan.[41] Examples of these and other opportunities for pharmacogenetics are highlighted below.

Perhaps the best example of a successful pharmacogenetic association, for which the clinical relevance is clear, features the management of treatment with warfarin.[42] The oral anticoagulant warfarin is prescribed for the long-term treatment and prevention of thromboembolic events, with more than 21 million prescriptions annually in the United States alone. However, because of the drug's narrow therapeutic index, a variety of complications is associated with its treatment, even after dose adjustment according to age, gender, weight, disease state, diet, and concomitant medications. An investigation of pharmacokinetic and pharmacodynamic drug properties indicated the additive involvement of 2 genes in determination of warfarin maintenance dose. One of these genes encodes CYP2C9, which is responsible for most of the metabolic clearance (~80%) of the more pharmacologically potent *S*-enantiomer of warfarin. Both *CYP2C9*2* and **3* cause a reduction in *S*-warfarin clearance, with 10-fold variation observed from the genotype linked with the highest (*CYP2C9*1/*1*) to lowest (*CYP2C9*3/*3*) activity. Numerous studies have associated these genotypes with initial dose sensitivity, delayed stabilization of maintenance dose, delays in hospital discharge, and increased bleeding complications. However, it is estimated that *CYP2C9* variants account for only 10% to 20% of the total variation in warfarin dose, with additional genetic and environmental factors playing larger roles in dose determination. The second gene identified as a predictor of dosing is the vitamin K epoxide reductase complex protein 1 (VKORC1), targeted by warfarin. A consideration of the *VKORC1* genotype or haplotype together with *CYP2C9* genotype and factors such as age and body size are estimated to account for 35% to 60% of the variability in warfarin dosing requirements.

Even though multiple independent groups have reproduced these data, prospective clinical studies are required to establish whether the initial dose may be tailored to patients by *CYP2C9* and *VKORC1* genotyping, coupled with known clinical variables. Although these studies are currently under way, the clinical pharmacology advisory panel to the U.S. Food and Drug Administration (FDA) acknowledged the importance and potential for genotyping of CYP2C9 and VKORC1 during the early phase of warfarin therapy, and the drug label was amended accordingly in August 2007.

A form fruste of pharmacogenomics is the notion of ''targeted therapies.''[43] Trastuzumab therapy (a monoclonal antibody specifically targeting HER2/*neu* overexpressing breast tumors) is an example of a protein therapeutic for which an obligatory biomarker assay and diagnostic test has been developed to identify the patients most likely to benefit from this drug. Trastuzumab is marketed solely for the subset of patients (~10%) who overexpress HER2/*neu*. Given the low prevalence of marker-positive breast cancers, it has been suggested that if it were not for the use of the diagnostic marker in clinical development, the drug would not have been successfully developed.

Cancer is not the only field of medicine with a targeted pharmacogenomic approach to giving therapeutics: For example, in cardiovascular medicine, a targeted approach to acute coronary syndromes has been practiced for more than a decade with the use of cTnI measurements to dictate the beneficial use of glycoprotein IIb/IIIa inhibitors. To assist clinicians in the practice of pharmacogenetics across a broad number of medications, the first microarray-based gene chip, approved both in the United States and European Union, was released in 2003 as the AmpliChip CYP450 (Roche Diagnostics, Indianapolis, Ind).[44] The product was

designed to identify key genetic polymorphisms in 2 CYP450 enzymes, *CYP2D6* and *CYP2C19*, which are cumulatively responsible for much of the first pass metabolism of many currently prescribed drugs. The regulatory agencies cleared this test based solely on analytical performance and validity information but indicated its utility specifically for clinical application needed to be proven. Thus, clinicians remain unclear about the impact of these tests on clinical decision-making guidelines.

Can interpatient variability in somatic tissues such as an individual's tumor be used in treatment planning? Recently, a series of gene expression signatures have been developed that predict response and resistance to conventional cytotoxic chemotherapeutic agents, portending the advent of personalized cancer treatment based on a tumor's gene expression pattern. Using *in vitro* drug sensitivity data combined with microarray gene expression data publicly available for the NCI60 set of cell lines, the signatures of response to cis/carboplatin, docetaxel, paclitaxel, topotecan, adriamycin, 5-FU, cyclophosphamide, and etoposide were developed using logistic regression modeling.[45] Using independent sets of human tumors with a known clinical outcome and for which expression data were available, the authors went on to demonstrate that these signatures could predict response to chemotherapy in these tumors in both the neoadjuvant and adjuvant chemotherapy settings. These genomic signatures now form the basis for a series of ''first of their kind'' clinical studies in which treatment assignments in the trials are being made on the basis of pharmacogenomic molecular signatures from a patient's tumor. This is perhaps one of the clearest examples of a genomic technology paving the way for truly personalized medical treatment.

Monitoring. The use of peripheral blood mononuclear cell (PBMC) gene expression profiling has made tremendous progress in the area of solid organ transplantation, with much of the effort focused on developing better tests for predicting graft rejection.[46-48] Research in cardiac transplantation, perhaps more than any other organ, led the way in developing novel blood-based tests for distinguishing between quiescence and acute rejection. CARGO, which is a landmark 3-phase, multicenter study in the area of cardiac transplantation, showed that PBMC gene expression profiling could be used to distinguish accurately between posttransplant patients in quiescence versus acute rejection.[49] This was achieved by first identifying a set of 11 genes that best distinguished between acute rejection and quiescence and then using an independent cohort to validate the classifying scheme in a prospective and blinded manner. Using a scoring system from 0 to 40, with low scores representing low-risk for graft rejection, researchers set 20 as a threshold for rejection and found that this criterion gave an 84% concordance with a pathologists' reading of grade 3A/2R and a 38% concordance with quiescence or grade 0 biopsy. However, using a threshold of 30 on patients more than 1 year posttransplant, validation of the test yielded a 99.6% negative predictive value and 6.8% positive predictive value for acute rejection. This test is commercially available as Allomap (XDx; Brisbane, Calif) and costs roughly $3000 per test. Although it is expensive, a cost analysis based on data from the CARGO cohort has shown that this blood-based gene expression profiling test is cheaper than biopsy and is likely to save as much as $12 million in health care costs annually.[50] For this to be true, however, the need for biopsy would have to be obviated and gene expression profiling would have to suffice in patients considered ''low risk'' for rejection. Toward that end, a prospective, multicenter, randomized but nonblinded trial called The Invasive Monitoring Attenuation Through Gene Expression has been initiated. The main hypothesis of the study is that a primarily noninvasive rejection surveillance strategy using gene expression profile testing is not inferior to endomyocardial biopsy in diagnosing cardiac allograft dysfunction in rejection and hemodynamic compromise along with all-cause mortality. Should this study show favorable results, it would represent a key example where PBMC gene expression profiling can be used practically to guide therapeutic decision making in real time.

PERSONAL GENOMICS

At the heart of the genomic approach to personalized medicine will be information from individual genomes, which is a fast-moving area of technological development that is spawning a social and information revolution among consumers. Dramatic improvements in sequencing technology[51] have reduced the cost and time of resequencing projects to a level that invites conjecture about the long awaited ''$1000 genome.''[52-54] The advances in single-nucleotide polymorphism (SNP) technology that are providing insightful gene association data also are allowing a glimpse at variation in our personal genomes and at low cost. Direct-to-consumer initiatives to make the variation in one's genome available in the form of SNPs at specific loci for $400–$2500 have been announced by several companies. These initiatives use the 500K–1000 K SNP Chip or similar technologies. They report information back to their customers on 20–80 areas of the genome that have been identified as disease risk susceptibility loci, and some offer additional information such as one's ancestry. This may be a ''disruptive technology'' for health care delivery with the provision of health and disease risk information to consumers without physician intervention and guidance. It

Table III. Regulatory policy supporting genomic and personalized medicine

Policy	Action	Reference
Guidance for Voluntary Genomic Data Submissions	Provides safe harbor for pharmaceutical firms to submit molecular data to FDA for discussion and evaluation.	58
Draft guidance for pharmacogenetic and other genetic tests, including microarrays	Provide standards for genetic testing and multiplex testing (eg, microarrays).	59
Concept paper for the co-development of pharmacogenomic drugs and diagnostics	Develops a framework for the development of combination products.	60
Adaptive clinical trials	Encourages innovation in trial designs aiming for enrichment in certain molecularly defined patient populations.	61
Draft Guidance for In Vitro Diagnostics Multivariate Index Assays	Creates a new classification of devices called IVDMIAs, which are a subset of laboratory developed tests. IVDMIAs would be subject to the full device regulatory scheme, including the need for FDA clearance or approval.	62

Abbreviation: IVDMIA, in vitro diagnostics multivariate index assays.

will not be long before a patient will bring a report of a whole genome to a physician's office and ask for guidance. What will the physicians of today, who are typically armed with a paucity of genomic training, tell them?

Some in the medical community have called personal genome scans premature and ill advised,[55] and similar concerns have been raised for more traditional and less comprehensive commercial tests targeted to specific genes or to specific conditions.[56] Hesitation on the part of health professionals aside, however, it seems clear that at least some consumers, whatever their motivations, will choose to test their genomes, regardless of whether any findings are (yet) considered actionable by their physicians. This creates both the need and an opportunity for health professionals to stay abreast of the rapidly developing scientific foundations of genomic medicine, to place in context the dynamic and still poorly understood interplays of the genome with the environment, and to communicate effectively the complexities of overall genetic risk to their patients.

INTEGRATION OF GENOMIC TESTING INTO CLINICAL PRACTICE

Despite the optimism expressed regarding the impact that genomic testing might have on medicine, many barriers must be overcome to their integration into clinical practice. That the incorporation of genetics and genomics into patient management guidelines has largely failed to occur thus far can likely be attributed to 3 realities. First, researchers, diagnostic firms, and the regulatory authorities are still seeking to establish methodologies by which to judge their effectiveness. Second, practicing clinicians and guideline writers are still working to understand how such new tests fit into current models of care and risk assessment, and, third, payers are just beginning to foresee new pressures to cover the additional costs. A framework has been proposed to assist in genetic testing evaluation,[57] establishing (1) the technical capabilities and operational standards of the test(s), (2) the diagnostic capabilities and impact on clinical decision making, (3) how the test will be integrated with existing physician behaviors and norms, (4) cost effectiveness, and (5) health outcomes.

Policy change is required for system-wide adoption. Although scientific findings are making their way from the genome to the clinic, the full application of genomic and personalized medicine in health care will require dramatic changes in regulatory and reimbursement policies as well as legislative protections for privacy.

Regulatory policy. The FDA has embraced genomic and personalized medicine as an important solution to an unsustainable pharmaceutical industry model for drug development. Several proactive and important steps have been taken that embrace the emerging practice of personalized medicine (see Table III[58-62]).

The list of diagnostic tests on the label for drugs approved by the FDA is growing as has the number of pharmaceutical products with package inserts recommending a genetic test for prescription selection or dosage.[41] Now more than 200 product labels either recommend genetic testing or point to the influence of genetic variation on drug response or safety.

Reimbursement policy. One of the most important factors influencing the integration of personalized medicine is the cost of the tests and treatments and whether public and private insurers will be willing to reimburse those costs. If the Centers for Medicare and Medicaid Services (CMS) and large insurers start paying for genetic tests to guide the prescription of companion drugs or for the prevention or management of chronic diseases, then personalized medicine will have reached a turning point. Coverage with evidence development and reimbursement for personalized medicine products will set the stage for the collection of large amounts of real-world

Table IV. Reimbursement policies supporting genomic and personalized medicine

Policy	Action	Reference
The Advanced Laboratory Diagnostics Act of 2006	Ensures that the payment system more accurately reflects the value of molecular diagnostic tests and their potential to reduce health care costs in the long run.	64
The American Association of Health Plans	Advocates a policy of encouraging genetic testing and preventive care, even for presymptomatic individuals when those tests can lead to improvements in care.	65
CDC ACCE Project	A model process for evaluating data on emerging genetic tests based on analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social issues.	66
Evaluation of Genomic Applications in Practice and Prevention	Evaluation of genetic and genomic tests and establish standards for what constitutes adequate evidence for insurance coverage.	67

Abbreviation: CDC, Centers for Disease Control.

Table V. Legislative policies supporting genomic and personalized medicine

Policy	Action	Reference(s)
Genetic Information Non-Discrimination Act (GINA)	GINA ensures that all genetic information will be protected against misuse in health insurance and employment.	68
HHS Personalized Health Care Initiative	Designed to improve the safety, quality, and effectiveness of health care for every patient in the United States.	69
Genomics and Personalized Act	Developing the potential of personalized medicine to improve the quality of health care and the policy changes needed to create a more accommodating landscape for it to thrive.	70, 71

Abbreviations: HHS, health and human services.

data and comparative effectiveness research that may provide subsequent evidence of their benefits and cost savings. However, insurers have stated that they have little incentive to support reimbursement for genetic tests because there is often such a high membership turnover rate that they cannot reap the long-term cost benefits of prevention that might result from genetic testing.[63] The CMS rules for Medicare state that ''tests for screening purposes that are performed in the absence of signs, symptoms, complaints, or personal history of disease or injury are not covered except as explicitly authorized by statute.''[63] Such a policy will have to be modified to make full use of predictive screening tools offered by personalized medicine, including one time tests (such as a CYP450 test for drug metabolism) that provide data that may be used for many pharmacogenomic applications relevant during a patient's lifetime of health care. Several initiatives in the past 5 years indicate, however, that the payment policies of both public and private insurers are beginning to move toward supporting personalized medicine (see Table IV[64-67]).

Legislative initiatives. Personalized medicine is a priority health care issue for the United States and other governments. The enactment of a genetic privacy law, a department-wide initiative in HHS, and a bill introduced in Congress specifically for the support of personalized medicine all attest to the interest and actions of policy makers (see Table V[68-71]).

We Will Have Arrived When "Personalized Medicine" is "Medicine". The human genome sequence is now available and is accessible to many. It is important to acknowledge that our knowledge of the genome and its biologic complexity is nowhere near complete, and new finding and insights into the role of genomics and disease are reported daily. Genomic protocols are being tested in practice environments in a few institutions that will doubt pave the way for others to embrace their use in standard clinical care. There are many challenges both from a scientific and policy perspective, which will be confronted and solved with the certainty that the science behind genomic medicine is sound and the practice of medicine that it informs is evidence based. As eloquently stated by HHS Secretary Kathleen Sibelius:

> If we are to achieve higher quality care for all Americans at a sustainable cost, we must look to those changes that improve the productivity of healthcare in the same way that we see quality gains traveling hand-in-hand with lower costs in other sectors throughout our economy.

> Personalized medicine seeks to use advances in knowledge about genetic factors and biological mechanisms of disease coupled with unique considerations of an individual's patient care needs to make healthcare more safe and effective. As a result of these contributions to improvement in the quality of care, personalized medicine represents a key strategy of healthcare reform. The potential application of this new knowledge, especially when supported through the use of health information technology in the patient care setting, presents the opportunity for transformational change. Today, it is common for a medical product to be fully effective for only about 60 percent of those who use it. As the medical community is now learning, this in part reflects biological variation among individuals that affects the clinical response to medical interventions. In the past, they have not had the tools or knowledge to understand those differences. In the future, when doctors can truly prescribe the right treatment, to the right person, at the right time, we will have a new level of precision and effectiveness that will provide the knowledge-driven power that is necessary to achieve our highest goals in healthcare reform—including more effective disease prevention and early disease detection.
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> *Testimony given during Senate confirmation hearings, April 2, 2009*

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