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## Genetics and Cardiovascular Disease A Policy Statement From the American Heart Association

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Although the power of family history to identify a genetic predisposition to disease has been appreciated for some time, it is only recently, through the development of efficient methods for molecular genotyping and specific genetic tests, that a detailed genetic evaluation could be used to influence clinical medicine. Indeed, the mapping of the human genome and the more recent development of high-throughput methodologies have the potential to entirely transform how we think about genetic predisposition to disease. This represents a great opportunity to improve human health. Yet these recent technological advances also create new moral, ethical, and legal challenges that must be addressed before the opportunities to improve human health can be fully realized. In the present report, we summarize the existing regulatory landscape with respect to the use of genetic information in clinical medicine and offer new policy recommendations designed to facilitate the safe incorporation of the latest technologies and research findings into the clinical domain. Specifically, we focus on areas in which genetic evaluation, including personal and family history, examination, counseling, and testing, has the potential to impact the practice of cardiovascular medicine and research.

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## The Legal Status of Genes and Genetics

### Gene Patents

Patent law is enshrined in the US Constitution in Article I, Section 8, and the principles imply that to be patent eligible, an invention needs to demonstrate novelty, utility, and nonobviousness. As such, although the patenting of raw naturally occurring materials has been generally rejected, where significant innovation is involved in its isolation, the patent office has generally granted protection (for example, insulin and adrenaline). In 1980, the US Supreme Court deemed a living organism patentable (*Diamond v Chakrabarty*) if “man-made,” as potentially accomplished via genetic engineering. In the wake of this decision, the US Patent and Trademark Office (USPTO) began to approve applications with DNA sequences central to the patent claim, initially for man-made vectors, but subsequently for human genomic DNA that had merely been isolated and purified. Central to the claim of such gene “patents” was that an isolated and purified gene (or synthetic gene) is different from its naturally occurring counterpart. Holders of these patents asserted that patenting isolated compounds was a practice essential to the growth of the US biotechnology industry.

The patenting of genes since the 1980 landmark decision by the Supreme Court has not been without controversy. Critics have argued that the USPTO has been too liberal in its approval of gene patents, saying that many of these patents are inappropriate because they merely represent observations of naturally occurring DNA sequences. They claim that the actions of the USPTO hinder research, because scientists are restricted in the research they can perform on DNA associated with patents. Similarly, they also suggest it might impair the use of the patented genetic material in clinical testing procedures and ultimately the affordability of and access to care.

In recent years, this issue has received interest in Congress, with legislation introduced that would restrict the practice of the USPTO in issuing gene patents. More significantly, the validity of some of these gene patents has been challenged in federal court, leading to renewed uncertainty of the patentability of the  $\approx 20\,000$  genes in the human genome. With a large number of human genes currently subject in some way to patent protection, court decisions on intellectual property law with regard to DNA patents may have profound implications for the delivery of personalized medicine.

### Myriad Genetics, Inc: History and Ruling

Although not representative of the vast majority of patent claims in the genomic space, arguably the most controversial gene patents are those currently held by Myriad Genetics, Inc (Myriad) that cover the methods and materials used to (1) isolate and detect the human breast and ovarian cancer–predisposing gene *BRCA1*; (2) isolate and detect the human breast cancer–predisposing gene *BRCA2*; (3) screen the *BRCA1* and/or *BRCA2* genes for mutations; and (4) facilitate diagnosing the predisposition to breast (both *BRCA1* and *BRCA2*) and ovarian (*BRCA1*) cancer. Myriad’s patents have positioned them as the sole entity entitled to offer genetic testing for the diseases based on the *BRCA1/BRCA2* genes. Furthermore, the Myriad patents prohibit other laboratories from testing clinical gene variants that are not part of the Myriad test, which puts restrictions on medical professionals working to determine patients’ risk of disease. The scope of the patents, how Myriad has enforced these patents, and the subsequent impact of these patents on clinical care and research recently led to a challenge in the US District Court for the Southern District of New York by the Association of Molecular Pathology (AMP) and the American College of Medical Genetics and others, with support from other groups including the American Medical Association and the American Society for Human Genetics (*AMP v USPTO*). The suit was filed by the American Civil Liberties Union and the Public Patent Foundation, and

on March 29, 2010, Judge Robert Sweet issued a landmark decision that invalidated many of Myriad's patent claims on *BRCA1* and *BRCA2*. Myriad appealed Judge Sweet's decision in the Court of Appeals for the Federal Circuit. Of note, despite the US Department of Justice submission to the appeals court that although man-made compositions such as complementary DNAs, vectors, and recombinant plasmids may be appropriate for patent protection, "genomic DNA that has merely been isolated from the human body, without further alteration or manipulation, is not patent eligible," the Federal Circuit recently overturned the district court decision and confirmed that isolated DNA molecules are patent-eligible subject matter because they "have a distinctive chemical identity and nature ... from molecules that exist in nature." Of note, however, claims that included only steps of analyzing and comparing DNA sequences were found not to be patent eligible, which creates uncertainty. At the center of the decision was a view of DNA as chemical. Critics have argued that a chemical view ignores the constantly changing chemical environment of the body and that it is the biochemical function of DNA that is most relevant. At the time of this writing, a biparty appeal had been denied and an appeal to the Supreme Court lodged.

**Patents on Genes With Significance for Cardiovascular Disease**—There are many patents associated with genes linked to cardiovascular disease (CVD) but few that have directly impacted the availability of genetic testing. One example is the long-QT syndrome (LQTS), a disease responsible for a small but significant fraction of sudden deaths in young people. Genetic testing for LQTS has an important influence on decisions about preventive care and pharmacological therapy. The major LQTS susceptibility genes were discovered at the University of Utah in the mid-1990s with funds provided by the National Institutes of Health (NIH). The University of Utah began licensing patents on LQTS susceptibility genes, with most patents controlled by Clinical Data, Inc, and its subsidiary PGxHealth. For many years, Clinical Data was the only laboratory offering LQTS genetic testing in the United States. Bio-Reference Laboratories Inc entered the market in early 2009, expanding the number of commercially testable genes.<sup>1</sup> Although it seems likely that the University of Utah patents delayed the entry of competitors into this particular market, it is not clear that patient care was affected.

**Policy Recommendations**—The case for gene patents fundamentally rests on the notion that isolated DNA is distinct from its existence in nature. Although few would debate that methodologies for manipulating DNA in cells for functional use should be eligible, as scientists we do not believe the breaking of covalent bonds that occurs in the isolation of DNA to read sequence reaches a standard of manipulation sufficient to demonstrate novel function. Nor do we believe that the historical view, either from the biotechnology industry or from the USPTO, should be our guide for a question that is fundamentally about the biological function of DNA; what may have been nonobvious in previous years cannot be held to be nonobvious now. We believe that although more liberal nonexclusive licensing practices should be encouraged as a primary approach to this issue to promote the rapid diagnosis and treatment of cardiovascular disorders, further patenting of DNA sequences should not be approved in cases in which the "invention" involves the observation of functionally unaltered human DNA.

### The Genetic Information Nondiscrimination Act

Declared "the first major new civil rights bill of the new century,"<sup>2</sup> the Genetic Information Nondiscrimination Act (GINA) was signed into law by President Bush in 2008. The new law protects the public against health insurance or employment discrimination that is based on genetic information, defined as information about genetic tests of individuals and their relatives, as well as family history. Group health plans and issuers of health insurance, whether providing group or individual coverage, may not use genetic information for the

purposes of underwriting (for instance, denying coverage or determining premiums). Similarly, an employer may not base hiring, firing, or promotion decisions on the genetic profiles of employees or potential employees or members of their families. The law not only protects against discrimination but also greatly restricts access to an individual's genetic information by employers or providers of health insurance.

The passage of GINA was important for research and the increased use of genetic tools to enhance health care. In foreseeing a future of personalized medicine in which genetic testing is commonplace, a significant fear among the public has been that undergoing genetic testing,<sup>3,4</sup> or volunteering in clinical trials to develop new genetic tests, can lead to the disclosure of their genetic information, leaving them vulnerable to discriminatory practices in the workplace or through their health insurance. Indeed, an early champion of establishing protections against genetic discrimination was the current director of the NIH, Francis Collins.<sup>5</sup> Therefore, one of the purposes of the law is to reassure patients that they can take a genetic test or volunteer to be a participant in genetic and genomic research without recourse.

Although GINA was signed into law in 2008, the regulations determining how it will be implemented were only finalized in November 2010. It is therefore too early to evaluate its effect in encouraging the public to volunteer for clinical trials that involve genetic testing. Public education will be an important component of its implementation if the law is to be successful in this regard. A recent survey<sup>6</sup> found that only 16% of Americans are aware of any law that protects the privacy of their genetic information. Perhaps not surprisingly in light of this result, it found that 71% of Americans are concerned about providers of health insurance accessing their genetic information. The survey also found that 81% of physicians are unaware of GINA. In the absence of education of the public and the medical community, the effect of the law as a catalyst for the recruitment of research volunteers will likely be limited. Beyond this, implementation is unlikely to lead to overt changes in the health insurance industry or the workplace, because providers and employers already claim they do not base decisions on this information.

Because the purpose of GINA was to limit discrimination based on genetic information, it does not extend to prohibiting health insurance providers from using patient health or disease history to make health insurance coverage and underwriting decisions. Whereas, for instance, GINA stops an issuer of health insurance from denying coverage to a person because they have a gene variant that increases their risk of having a condition, it does not prevent the provider from denying coverage to a person who has been diagnosed with the condition. However, this gap in patient protections was filled with the passage of the Affordable Care Act. When the law is fully implemented in 2014, the Affordable Care Act will require that group health plans and issuers of health insurance provide coverage for all individuals who request it. Providers will not be able to use a patient's health status or medical history to determine coverage, and ratings based on enrollees' health status will be prohibited. Indeed, this is already in effect for minors: Health insurance plan years starting after September 23, 2010, may not reject children under 19 years of age because they have a preexisting condition (although that this does not apply to grandfathered individual health insurance policies that existed before the Affordable Care Act was signed into law).

**Policy Recommendations**—The available data suggest that most Americans, including physicians, are not aware of GINA or the protections it affords. GINA will have a greater effect in public willingness to volunteer for genetic research if educational campaigns that target the medical community and the general public can be implemented.

Although GINA protects the public in those areas in which the fear is known to be greatest, the American public is not completely protected against all forms of genetic discrimination. For instance, there is no protection against the basing of life insurance underwriting on family history. Similarly, there are no protections with respect to long-term care insurance or disability. To maximize the development and utility of genetic testing in health care, it is important that the federal law address this area to ensure that patients can undergo such testing without financial or other penalty.

In addition, we reaffirm the previously stated view of the American Heart Association that protection from discrimination should be afforded to all patients based not simply on genetic risk but also on actual health status and prior health history. Such provisions protecting patients from discrimination are outlined in the Affordable Care Act.

### **Current Policies and Debate on Genetic Testing**

In June 2010, the US Food and Drug Administration (FDA) announced its intention to regulate all laboratory-developed tests, including genetic tests. To date, the agency has regulated tests sold as testing kits, but in general, tests performed in a laboratory have been marketed without the need for clearance or approval from the FDA. Laboratories conducting genetic testing for clinical care are required to comply with the Clinical Laboratory Improvement Amendments (CLIA) program run by the Center for Medicare and Medicaid Services (CMS), but this program does not assess clinical validity (whether individual tests performed are medically meaningful). Although the FDA has had the authority to regulate laboratory-developed tests because these are medical devices as defined by federal law, it has to date practiced what it calls “enforcement discretion.”

The FDA’s announcement is the latest stage of a policy discussion that began over a decade ago. With the increased marketing of genetic tests, concerns have been raised repeatedly that without any independent examination, medical professionals and patients have no assurance of the value and limits of each genetic test. Several bodies have examined the issue and called for stronger oversight.

In 1997, a joint report of the NIH and the US Department of Energy provided several recommendations to ensure the safety and effectiveness of genetic tests<sup>7</sup> and proposed that the Department of Health and Human Services set up a standing advisory committee on genetic testing. The Secretary’s Advisory Committee on Genetic Testing that was established as a consequence issued a report in 2000 entitled, “Enhancing the Oversight of Genetic Tests.”<sup>8</sup> Among its conclusions, the committee recommended, “No test should be introduced in the market before it is established that it can be used to diagnose and/or predict a health-related condition in an appropriate way. Thus, the public is best served by ensuring both the adequate oversight of genetic tests and the continued development of genetic tests.” It further stated that “the FDA should be the federal agency responsible for the review, approval, and labeling of all new genetic tests that have moved beyond the basic research phase.”

The Department of Health and Human Services did not implement the recommendations of the Secretary’s Advisory Committee on Genetic Testing, but concerns continued to be expressed about tests coming to market without independent verification. In 2006, the Government Accountability Office released a study of 4 companies that offered genetic testing services directly to consumers.<sup>9</sup> Although the companies claimed that their tests could indicate future risk of chronic diseases such as type 2 diabetes mellitus, heart disease, and high blood pressure, the Government Accountability Office concluded that the results given to consumers were medically unproven, meaningless, and misleading. The Federal Trade Commission issued a statement to warn the public of at-home genetic testing, saying



that the public should “Be wary of claims about the benefits these products supposedly offer.”<sup>10</sup> In a 2006 hearing of the Senate Special Committee on Aging on this issue, then-Senator Gordon Smith (R-OR) referred to misleading tests as “modern-day snake oil.” The following year, Senator Smith introduced the Laboratory Test Improvement Act with then-Senator Edward Kennedy (D-MA) to set up a framework for FDA review of laboratory-developed tests. Then-Senator Barack Obama (D-IL) also introduced legislation that addressed the issue.

In 2008, the successor to the Secretary’s Advisory Committee on Genetic Testing, the Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS), issued a new report on genetic testing oversight in response to a request from the Secretary of the Department of Health and Human Services.<sup>11</sup> Consistent with previous reports, the committee expressed concern about the gaps in oversight related to clinical validity and said that the “FDA should address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests,” as well as recommending the establishment of a mandatory test registry.

In 2010, a Government Accountability Office investigative report<sup>12</sup> was released in conjunction with a hearing of the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce in the US House of Representatives. The committee investigated 4 other companies that marketed genetic tests directly to consumers and provided direct access to genetic testing services. The Government Accountability Office again found variability in the results delivered and the advice offered and found that the companies were misleading customers, concluding that the test results offered by these companies were of “little or no practical use.”

**Policy Recommendations**—We believe that all genetic tests, including laboratory-developed genetic tests, should be required to undergo independent review to confirm their analytic and clinical validity and that this information should be made available to healthcare professionals and the public at large. This is consistent with the recommendation from the SACGHS, the directors of the NIH, and the FDA<sup>13</sup> and is similar to the current requirements for tests marketed as kits.

The appropriate regulatory framework for ensuring that these requirements are met for laboratory-developed tests is an area of ongoing debate. The CLIA laboratory certification program includes some proficiency testing, but there is no independent scrutiny of the clinical validity of tests. Historically, most genetic laboratory-developed tests aimed to identify rare genetic features in an environment where the risk of a false or misinterpreted result was relatively low. However, technology advances have led to the development of more complex genetic tests involving multiple genetic features, some commonly found in the population. Because of the moderate-to-high complexity of many newer tests and their interpretation, testing requires the regulatory oversight by an authority capable of fully evaluating both the analytic validity and, especially, the clinical validity. As observed by the American Heart Association,<sup>14,15</sup> the FDA is ideally suited to perform this function, because it has the clear statutory authority, scientific expertise, and experience in regulating genetic tests. It would be essential that the agency be appropriately resourced to ensure efficient test review and continued access to tests with established clinical validity.

Finally, we note that the active involvement of clinical investigators and institutions in the development of genetic tests has created opportunities for conflicts of interest to arise when these same individuals or institutions are in the position to recommend these tests to healthcare providers or patients. We believe that all conflicts of interest with respect to genetic tests need to be fully disclosed and actively managed.

## Testing for Mendelian Disease

Mendelian disorders are the prototypical genetic disorders in which defects in single genes exert large effects in causing disease. In classic mendelian disease, characteristic patterns can be ascertained by careful interrogation of family history. Research efforts over the past 20 years have led to the identification of the genetic basis of conditions, such as hypertrophic, dilated, and arrhythmogenic cardiomyopathy; LQTS; and Marfan syndrome and related connective tissue disorders. Technical advances in DNA sequencing technology have allowed genotyping to evolve from a research tool to a commercially available diagnostic clinical test. However, the remarkable genotypic and phenotypic complexity of these disorders, including variable evidence to support the pathogenicity of identified variants, creates important considerations for genetic evaluation, including the appropriate implementation and interpretation of genetic testing.

Current genetic testing relies on direct DNA sequencing of candidate genes. Because cardiovascular genetic disorders have been associated with many different genes, thousands of individual mutations (missense, nonsense, insertion/deletion, and splice site), a high prevalence of novel DNA variants, and a 3% to 5% rate of double or compound heterozygosity (>1 DNA variant present in an individual), genetic testing must be comprehensive to have reasonable impact. This requires analysis of the full coding sequence and intron/exon boundaries of all genes robustly associated with the disease of interest, because individual variants tend to be specific (private) to each kindred. More limited forms of genetic testing, focusing on a smaller subset of genes or previously reported mutations, are not recommended, because they are of questionable clinical utility. The emergence of more rapid and inexpensive whole-exome or whole-genome sequencing methodologies will substantially improve the cost and feasibility of candidate gene sequencing in mendelian diseases in the near future. Additionally, by increasing the number of genes that can be analyzed simultaneously, these high-throughput methods will allow identification of gene-gene interactions and genetic modifiers that impact disease severity. New technology will also allow detection of other types of genetic variation, such as variation in the number of copies of DNA segments, that may contribute to disease but generally escape detection with current methods.

Genetic testing can uniquely complement standard clinical evaluation. The power of genetics lies in exquisite diagnostic accuracy (diagnostic testing) and preclinical identification of at-risk family members (predictive testing). For diagnostic testing, the identification of a variant convincingly tied to the disease in an affected individual independently confirms the clinical diagnosis and helps define the family's genetic substrate. The recommended strategy is to initiate genetic testing in the individual with the most unequivocal clinical diagnosis, because they are most likely to have a variant. The initiation of diagnostic genetic testing in individuals with more ambiguous phenotypes will be of lower yield and more difficult to interpret, because it may be difficult to assert unequivocally that an identified variant is causative for the phenotype. The current incomplete knowledge of all disease-causing genes poses an important limitation to diagnostic testing. Genetic testing of known candidate genes will be positive (ie, will identify pathogenic variants) in up to 70% of patients with both a clinical diagnosis and a family history of the condition of interest. In some situations, the yield may be far lower. As such, a negative genetic test result is largely noninformative, because it does not exclude the possibility of a specific disease nor does it exclude the possibility of a genetic process in the individual or family.

Once the family's genetic substrate has been identified, predictive genetic testing in relatives can provide substantial clinical impact and cost savings.<sup>16,17</sup> Focused DNA evaluation is

performed to determine whether the family-specific mutation is present or absent in other family members. This provides nearly 100% sensitivity and specificity to identify relatives who have inherited the genetic predisposition but who may not have developed diagnostic clinical features at the present time. Comparable information is not available without genetic testing because of false-negative and false-positive results inevitably associated with clinical evaluation alone. For example, clinical evaluation may miss individuals with subtle, late, or nonpenetrant disease features but who remain at personal risk for serious disease complications and/or who have children who would otherwise be unrecognized as being at risk for developing disease.

By incorporating predictive genetic testing into family management, longitudinal clinical follow-up for phenotypic development, risk stratification, and preventive treatment can be focused only on mutation carriers rather than on all family members. Relatives who have not inherited the family's variant may not require prospective screening, although clinical evaluation should be pursued in response to relevant changes in clinical status.

Predictive genetic testing also has valuable applications in reproductive planning. If the family's genetic substrate is known, advantage can be taken of preimplantation genetic diagnosis. With in vitro fertilization techniques and single-cell DNA analysis, attempts can be made to achieve a pregnancy with an embryo that does not carry the family's mutation, thus preventing the development of disease in that individual and their offspring.

Determining whether DNA variants are truly pathogenic and capable of causing disease is seldom straightforward because of the large amount of benign or poorly characterized genomic variation in human populations and the current lack of robust functional assays to confirm whether DNA variants impact protein structure or function. Therefore, until the key determination of pathogenicity is made, test results should not be used as the basis for management decisions for individual patients or to screen their relatives. This is particularly relevant for cases in which novel variants are identified but in which the absence of other affected family members precludes the assessment of cosegregation of the putative mutation with disease. Moreover, not all variants reported in the literature as being disease-associated may truly be disease-causing because of the limitations of studies on single probands and the lack of robust genetic support for pathogenicity. Careful consideration, including expert evaluation, should be given before clinical genetic testing is pursued in these circumstances, regardless of the commercial availability of testing. Finally, the interpretation of genetic test results will change as knowledge evolves. Periodic reappraisal is critical to ensure that clinical application keeps pace.

### **Policy Recommendations**

We strongly advocate the involvement of physicians and centers with expertise in cardiovascular genetics to guide the appropriate initiation, interpretation, and implementation of genetic testing. Such experienced centers are ideally positioned to assist with difficult management decisions, including when to pursue clinical genetic testing, how to interpret results, and how results may impact management of both the patient and the family. Cardiovascular genetics centers can evaluate entire family units to optimize the use of the family itself to assist with interpretation of genetic testing results (ie, coordinating segregation analysis to evaluate the pathogenicity of ambiguous variants). They will provide requisite pretest and posttest genetic counseling to ensure informed decision making, minimize potentially detrimental psychosocial effects of genetic testing, and optimize patient understanding. It is especially important that the sequencing of disease-causing genes be performed in CLIA-approved laboratories, because the usefulness of the results is entirely reliant on high sequence accuracy (technical/analytical validity).



The regulation of technical validity is critical, especially because of the emerging use of next-generation sequencing in the clinical arena. Next-generation sequencing approaches involving short reads have inherent limitations for certain important areas of the genome (eg, trinucleotide repeat regions). More globally, the regulation of analytical testing validity for mendelian CVDs poses a particular challenge for a regulating body, given the genotypic variability and complexity typically observed. Although a causal link between a specific gene and a specific disease is often well established, interpretation of the clinical significance of a particular variant is complex. In determining the significance of an observed variant in a patient, the healthcare team takes into account both family-specific and variant-specific factors. Because results are achieved not by the analysis of a single locus but by the interrogation of a large number of loci, it is untenable to determine the clinical validity of testing at a single locus in isolation. As we look to regulate genetic tests, we urge the regulatory agency to take into account the inherent complexity of the genetics of mendelian diseases.

Given the increasing availability of clinical testing for mendelian CVD, it is imperative that there be sufficient funding for research on the genetics of CVD, by the NIH and other funding agencies, to promote gene discovery, improve assessment of variant pathogenicity, refine genotype-phenotype correlations, and gain the necessary insights into disease pathogenesis that will ultimately allow transformation of the clinical management of inherited CVD.

## Pharmacogenomics

It is a given in clinical medicine that response to drug therapy varies among individual patients, and several decades' worth of work has identified and validated rare and common polymorphisms that contribute to this variability for specific drugs.<sup>18</sup> Indeed, common pharmacogenetic variants often explain much larger proportions of variability in drug action than do common variants that predict common diseases like myocardial infarction (MI) or atrial fibrillation. It seems reasonable to anticipate that one of the first widespread applications of genetic testing in large numbers of patients will be in the pharmacogenomic realm: Genetic testing may be used to predict efficacy, to predict adverse events, or to identify optimal doses for individual patients.<sup>19,20</sup> There are a number of practical barriers that need to be overcome to execute this vision, and many are shared with other types of genomic information that are beginning to be used clinically. These include the following:

- Availability of genotypic information at or very shortly after the time of prescription
- Refinement of levels of evidence to guide prescribers in using genetic variant information to alter the choice of drug or dose
- Delivering that advice in a timely and effective fashion, which almost certainly will require sophisticated electronic medical record (EMR) systems
- Educating prescribers and consumers that genomic data rarely provide black-and-white answers but rather alter probabilities of beneficial or adverse drug responses.

Understanding the mechanisms responsible for drug disposition ("pharmacokinetic" factors including absorption, distribution, metabolism, and elimination) and variable interactions of drugs with their pharmacological targets ("pharmacodynamic" factors) has been a traditional first step in identifying genetic variants associated with variable drug actions. Importantly, these critical determinants of drug action have not always been well defined when a drug reaches market. Indeed, the basic mechanisms whereby warfarin, clopidogrel, and tamoxifen exert their pharmacological effects and the modulation of those effects by genetic variants have only been defined since the drugs' marketing.

As in other areas of genomics, the study of variable drug actions is progressing from candidate mechanisms to genome-wide association study (GWAS) and other approaches. Interestingly, the GWAS paradigm, when applied to variable drug responses, has often identified common variants in genes already implicated by candidate approaches in variable drug actions.<sup>21</sup> This supports the idea that single variants can exert large genetic effects that actually translate to clinical utility. Like many other GWAS approaches, a substantial proportion of variability in drug action is left unexplained by common variation and clinical covariates, which suggests other, as yet unidentified contributors (including gene-gene interactions, rare variation, and non-genomic factors).

In 2007, the FDA began a program of systematically evaluating pharmacogenetic information relative to drug dosing and incorporating this information into drug labels.<sup>22</sup> The FDA views the label as an information tool, but of course, the incorporation of these statements has led to increased controversy and uncertainty within the practitioner community. Much of this reflects an incomplete knowledge base, the need for rapid and reliable genotyping if a pharmacogenetic strategy is to be used, uncertainties about exactly how best to act on genetic data, and availability of alternate strategies. Warfarin and clopidogrel are 2 examples of cardiovascular drugs for which the FDA has revised the product labels to include pharmacogenetic information, including some provision of suggestions to clinicians about how to use such information.

### Clopidogrel

It has only become apparent since clopidogrel was marketed that it undergoes variable biotransformation to an active metabolite to exert its P2Y<sub>12</sub> receptor inhibition. This process is mediated largely (but not exclusively) by *CYP2C19*, and it is now unambiguously clear that use of standard doses of clopidogrel in patients with *CYP2C19* loss-of-function variants is associated with an increased frequency of major adverse cardiovascular events and, in particular, of in-stent thrombosis among patients receiving drug-eluting stents.<sup>23,24</sup>

A GWAS investigating clopidogrel-induced inhibition of ADP-mediated platelet aggregation in a relatively small number of subjects (n = 429) identified the *CYP2C19\*2* loss-of-function allele as the major contributor to variability in this phenotype.<sup>25</sup> The study was conducted in the Amish, with extensive family structure; as a result, it was possible to estimate that variability in the trait included a large (73%) heritable component. However, *CYP2C19\*2* contributed ~ 12% to this variation. These data create a controversy with respect to the role of genotyping in clopidogrel therapy. Advocates argue that although outcomes are variable, they are clearly worse in individuals with variant genotypes.<sup>26</sup> Opponents point to the problem that variability in response to clopidogrel includes factors beyond *CYP2C19*; the cumbersome nature of genotyping, which necessitates ordering a drug, ordering a test with rapid and reliable turnaround, and revising drug dosing on the basis of test results; development of platelet function testing; and the availability of alternate therapies such as prasugrel or ticagrelor that do not appear to have single large gene effects.

### Warfarin

Variants in *CYP2C9*, the enzyme responsible for bioinactivation of the active *S*-enantiomer of warfarin, have been known and associated with decreased dose requirements and increased bleeding risk since the 1990s.<sup>27</sup> The actual pharmacological target for warfarin is now known to be encoded by *VKORC1*, and rare coding-region variants in the gene lead to relative or absolute warfarin resistance.<sup>28,29</sup> However, in addition to these rare variants, there are common polymorphisms in the *VKORC1* promoter that are functionally important (as assessed by liver mRNA abundance) and are known to contribute to ancestry-dependent

variability in warfarin dose requirement.<sup>30,31</sup> Together, *CYP2C9* and *VKORC1* variation contribute ≈40% to 50% to the variability in warfarin dose in white subjects.

The arguments for and against the incorporation of warfarin genotyping into the flow of health care are similar to those with clopidogrel. Available data support the idea that dose prediction, and perhaps adverse effects of warfarin therapy, can be reduced by dosing algorithms that include genetic variation.<sup>32</sup> Opponents point to the cumbersome nature of the testing (which again requires point-of-care genotyping), lack of compelling data attesting to decreased serious adverse events, and the availability of newer anticoagulation strategies that do not require testing of the international normalized ratio. The National Heart, Lung, and Blood Institute is currently conducting a study comparing pharmacogenetically based therapy to best clinical algorithm (COAG [Clarification of Optimal Anticoagulation through Genetics] trial).<sup>33</sup>

Thus, for both drugs, there is no doubt that genetic variants contribute importantly to outcomes, but the implementation of a genotype-guided treatment approach is not straightforward. For warfarin, dosing strategies based on genetic variation have been developed, whereas the best dosing strategy for clopidogrel in patients with variant genetics is less well defined.<sup>34</sup> A key requirement for both drugs is rapid, reliable genotyping coupled with point-of-care decision support advice; it is impractical to rely on physicians to remember recommended actions on the basis of delivered genotype information. In addition, for both drugs, functional tests (international normalized ratio, platelet function testing) provide information on dose adjustment once a patient is undergoing therapy, so the greatest value of genotyping appears to be in initial drug or dose selection. Finally, in both cases, newer therapies that at this point appear to lack major genomic contributors to variable action are becoming available. Despite these challenges, the contribution by genetic variants to the action of these well-studied, highly effective, and inexpensive therapies is large, and the incorporation of genetically informed prescribing into practice is therefore appealing, especially as barriers are removed with the availability of EMRs that contain genomic data and with the development of advanced decision support informatics.

Regardless of how the issues that surround these 2 agents play out over the next several years, the principle that genetic variation contributes to variable drug actions is likely to continue to play a central role in the way in which genetic information is deployed into the workflow of patient care. Indeed, the first fully annotated human genome sequence<sup>35</sup> includes hundreds of variants that have been associated (with various levels of evidence) with drug responses. However, in virtually no case is evidence from randomized clinical trials available to direct a physician on how to use this information. That said, many prescribing decisions are made empirically in clinical medicine without the requirement of this level of evidence: No physician would conceive of demanding randomized clinical trial evidence before decreasing the dose of a renally excreted drug in a patient with decreased renal function. For widely used therapies with important outcomes, randomized clinical trials may be desirable, although difficult to establish and interpret, especially if variant genotypes are uncommon or new variants are discovered in the course of a randomized clinical trial. For many therapeutic situations, the choice among multiple drug options is informed by nuanced and often subjective (on the part of the prescriber) perceptions such as likely compliance, cost, and potential for drug interactions or side effects. Pharmacogenetic markers that contribute to this calculus (which  $\beta$ -blocker? which antihypertensive agent? which antidepressant drug?) may be part of another mechanism for optimizing therapeutics. The prospect of cheap genomic sequencing coupled to advanced informatics capabilities makes the idea of guiding therapy by genotypes that are already available in the EMR (“preemptive genotyping”) a real possibility.

**Policy Recommendations**—Consensus on a given pharmacogenomic effect and its relevance for the drug in question is needed before a clinical action is recommended based on genotype. This will require input from multiple stakeholders, including professional societies, the FDA, the Pharmacogenomics Research Network, pharmacy benefits payers (including the CMS), and patients. To establish such consensus will require continued funding from the NIH and other bodies for ongoing research in this area. In addition, implementation will require federal assistance in fostering the development of health information technology, including the interoperability of electronic health records that include advanced informatics capabilities.

## Common Variants and Risk Prediction

A number of common CVDs have heritable contributions, among them coronary artery disease, MI, ischemic stroke, and atrial fibrillation. Indeed, each of these has been the subject of GWAS that have identified loci that are significantly associated with these traits. These studies, distinguished from previous candidate gene studies by their unbiased genome-wide approach and high bar for achieving “genome-wide significance,” support the concept that genotyping of selected common single-nucleotide polymorphisms (SNPs) in the clinical setting may permit better identification of inherited risk of common CVDs. Indeed, such genotyping panels are already being marketed to physicians and the general public.

Although numerous studies support the role of family history as a risk factor for certain CVDs, the patient interview as routinely performed in general practice suffers from limited reliability (this should be contrasted with the comprehensive, dynamic family histories determined by genetic counselors, who will often spend weeks chasing down important family medical records). Even in the Framingham Heart Study, patients were correct only 28% of the time when they reported a positive parental history of early-onset heart attack. A national survey sponsored by the Centers for Disease Control and Prevention showed that fewer than one third of respondents actively inquired about health information from their relatives, even though almost all considered knowledge of family history important. Another found that cardiovascular family history was the most poorly reported of 6 common heritable disorders.<sup>36</sup> A marker of heritable cardiovascular traits, family history suffers from other limitations. Accuracy relies on an unbroken chain of events: Phenotypic manifestation of the inherited predisposition, correct diagnosis in the affected relative, and precise recall of the condition by the patient. Variable penetrance and expression or unusual occurrence of CVD in younger patients can challenge our ability to derive true inherited risk. In addition, family history may simply be unavailable in some patients (adoptions, small families). On the basis of these considerations, genetic testing of common variants shown to be associated with CVD may, with validation from clinical studies, augment patient-reported family history of CVD by directly evaluating heritable traits.

## Clinical Utility of Common Variant Genotyping for Risk Prediction

Several key questions are relevant to the clinical utility of common variant genotyping for CVD risk prediction. These include:

- Can genotyping offer better prediction than standard risk assessment, including family history, and is this enhanced prediction clinically meaningful?
- Will the result of genotyping change the patient’s management?

For purposes of illustration, we will use prediction of coronary artery disease/MI to highlight the issues involved. GWAS have identified many distinct loci that have genome-wide significance for an association with coronary artery disease or MI. The first locus to be identified, and one that has been consistently among the strongest with regard to

significance, is the locus at chromosome 9p21.3, associated with a 20% to 40% heightened risk of coronary heart disease among white and East Asian populations. There is no doubt of the veracity of this repeated observation, yet many question the clinical utility of genotyping a common variant that provides information of relative risk of only up to  $\approx 1.4$ . Nevertheless, it is appropriate to ask how knowledge of this genotypic information could influence clinical management. Investigators from the Atherosclerosis Risk In Communities (ARIC) cohort showed that the incorporation of a 9p21.3 SNP into clinical risk assessment improved discrimination, increasing the area under the curve from 0.782 to 0.786 (95% confidence interval for the increase 0.001–0.007) and yielded a clinical net reclassification index of 6.8%. Although this is a small change, a reclassification from moderate to high risk based on genotype result could lead to changes in clinical management, such as the decision to initiate statin therapy for a borderline low-density lipoprotein cholesterol level. An 8-SNP panel for prediction of MI risk is currently being marketed by one company (deCODE). The maximal increase in relative risk with this panel is  $\approx 70\%$ , which in concept could be sufficient to alter clinical management. A parallel strategy is to identify sets of common independent risk variants that individually confer modest risk (eg,  $<1.5$ -fold) but together may markedly increase in small sets of subjects. One study found that 3 unlinked SNPs at chr4q25 can identify  $<2\%$  of the population at  $>5$ -fold risk of atrial fibrillation.<sup>37</sup>

### Challenging Features of Common Variant Genotyping for Risk Prediction

The introduction of common variant genotyping for CVD risk prediction into clinical practice faces a number of hurdles. First, modest hazard ratios for individual SNPs, or even panels of SNPs, and the minor changes in receiver operating characteristic curve areas create skepticism about the clinical utility for risk prediction. Simply expanding the number of common SNPs in panels is unlikely by itself to address this issue. On the other hand, ongoing discovery of low-frequency variants that have a greater effect size on risk and the inclusion of selected variants in panels may increase hazard ratios and address this issue. Second, additional SNPs associated with common CVDs are being identified at a rapid pace. This has the effect of quickly making established genotyping panels seem obsolete, thus diminishing enthusiasm for genotyping “now” and instead resulting in the desire to wait for a “better” panel in the future (one that may include updated risk associations even for variants included in both panels). Third, it is not always clear how the genotype results can or should influence clinical management. Critically, no clinical trials have been performed that demonstrate the benefit of genotyping in influencing clinical outcomes. Fourth, interpretation of results can be challenging and time consuming for clinicians and patients alike, and the return of results to patients could be a major deterrent for clinicians in ordering genotyping for CVD risk prediction. Fifth, genotyping healthy individuals for future CVD risk in a clinical setting carries potential risks, such as limiting qualification in the future for life insurance or long-term disability insurance. Sixth, it remains unclear how payers will react to covering the costs of “predictive genotyping” in this setting. Despite this, knowledgeable clinicians might reasonably choose to perform genotyping for MI risk in patients for whom they believe their clinical management might be influenced by the outcome.

**Policy Recommendation**—Although robust GWAS evidence exists linking common variants to complex CVD, studies are not yet available to inform the clinical benefit of providing such genetic information to patients. Funding for such clinical studies is essential to build an evidence base for the field. Meanwhile, clinical consensus should be built to allow rational incorporation of additive genetic risk information to the clinical workup.



## Payer Perspectives

As the importance of genomic data for individual health begins to emerge, insurers have begun to define what will and will not be covered under standard health insurance. As is often the case with health care and technological advances, the situation is complicated, with different stakeholders having different positions on genetic testing depending on the specific circumstances. Insurers may be reluctant to cover new genetic tests until specific scientific standards are met, in part because of the high price tag. On the other hand, genetic tests that can predict individual response to, tolerance of, or adverse events from medication exposure may be more readily adopted if they are seen as resulting in the avoidance of unnecessary risk and expense. Indeed, the SACGHS concluded, “Although advances in genetics and genomics are driving the development of new genetic tests and services, problems with coverage and reimbursement are limiting their accessibility and integration into the health care system.”<sup>38</sup> Nearly 5 years later, many barriers remain.

Many commentators agree that any test to be covered should satisfy a test of clinical utility; however, no consensus exists as to what constitutes clinical utility, and there is a lack of clear guidance as to what the appropriate level of evidence should be.<sup>39</sup> The NIH plans to launch a genetic test registry that provides consumers, healthcare providers, researchers, and payers information on available genetic testing, including the specific laboratories offering testing and data on utility.<sup>40</sup> This registry is currently voluntary, although many, including payers, believe that a mandatory registry would be more useful.

In 2008, a workshop of stakeholders including insurers convened and concluded that determination of clinical utility was crucial to the appropriate integration of genomics into health care and that this process should take advantage of risk-benefit modeling that was “iterative, transparent, and parsimonious” to rapidly and critically assess genetic tests for clinical application.<sup>41</sup> The American Medical Association has recommended to the CMS the establishment of *Current Procedural Terminology* or “CPT” codes and reimbursement schedules for pharmacogenetic diagnostic services that will be in place in 2012. A 2-tiered system has been proposed and is being revised by the American Medical Association/*Current Procedural Terminology* editorial panel that includes 2 lists of older, more established tests and newer tests/tests under development.<sup>42</sup>

### Payer Perspective: Single-Gene Disorders

Genetic tests for highly penetrant single-gene disorders that are either diagnostic (in the presence of symptoms or signs) or predictive (in the absence of symptoms or signs in an at-risk individual) are usually covered by both CMS and private insurers. Specific insurers have developed criteria to determine whether a diagnostic genetic test will be covered.<sup>43–45</sup> In general, tests are covered if the test results have direct clinical implications for the management or prognostication of the individual and the test is validated both clinically (it diagnoses the disease with acceptable sensitivity, specificity, and positive and negative predictive values) and technically (it is reproducible and accurate). Diagnostic testing is generally covered for those individuals with clinical features of specific genetic diseases. Predictive testing is restricted to a single lifetime test in those known to be at risk on the basis of family history.<sup>46,47</sup> In cases in which familial disease-associated variants are known on the basis of test results from other family members, coverage is generally restricted to the known variants. In general, highly penetrant or treatable conditions are more likely to be covered. CMS coverage may differ by test such that if a test for a specific disease is only offered by a single laboratory and that laboratory is not a Medicaid provider, the test will not be covered (although some of the diagnostic laboratories have reduced rates for Medicare patients who are not covered<sup>48</sup>). Genetic counseling is uniformly recommended,<sup>49</sup> particularly when predictive genetic testing is performed; however, it is not uniformly

covered. Recent publications have demonstrated the negative outcomes that can occur when genetic testing occurs without adequate genetic counseling.<sup>50,51</sup> As of 2007, genetic counseling can be billed using a specific *Current Procedural Terminology* code (96040). To ensure access to genetic testing and appropriate use and interpretation of those tests, insurers will need to cover both the genetic test and the associated genetic counseling.

Hypertrophic cardiomyopathy has proven to be an important case study regarding coverage by insurers. In August 2010, Blue Cross Blue Shield published an analysis of genetic testing for predisposition to hypertrophic cardiomyopathy.<sup>52</sup> This “Technology Evaluation Center Assessment” delineated 3 scenarios that were used to clarify coverage: (1) A specific familial mutation is known and can be used as a screening test for unaffected family members; (2) no familial mutations are known, but affected family members are available for diagnostic testing; and (3) no familial mutation is known, and no affected individuals are available for testing. In condition 1, Blue Cross Blue Shield and Kaiser Permanente have agreed coverage is warranted. In condition 2, diagnostic testing of an affected family member may reveal an associated mutation and should be undertaken before predictive testing is considered. In scenario 3, in which no familial mutation is known and no affected family members can be tested (or family members have been tested and no familial mutation has been identified), testing is not recommended or covered. The report acknowledges that this is an evolving area and will need to be revisited in the future. Importantly, the sort of predictive genetic testing on at-risk family members that this report recommends is only feasible if a family member who has hypertrophic cardiomyopathy has diagnostic genetic testing first, yet the report does not indicate that such diagnostic genetic testing should be covered.

#### **Payer Perspective: Common Variant Tests**

Testing for a panel of multiple genetic variants that may influence risk for CVD remains an unrealized goal. To date, no insurance company has a specific policy on genetic risk panel testing, although some specifically exclude coverage of commercially available panels.

#### **Payer Perspective: Pharmacogenomics**

To date, none of the pharmacogenetic tests, including those with specific FDA labeling, are covered by insurance companies or by the CMS. Both in policy<sup>53</sup> and practice, FDA approval is almost always a requirement for, but not sufficient to ensure, Medicare coverage. Payers have identified antiquated coding as a substantial barrier in the development of coverage policies.<sup>54</sup> Among the drugs with specific mention of pharmacogenomic testing, warfarin and clopidogrel provide contrasting case studies (Table). Coverage is limited, but prospects for coverage appear to differ. CMS opened a National Coverage Assessment for pharmacogenomic testing for warfarin and determined that there was insufficient evidence to support the use of the test for dose determination. CMS agreed to cover the testing in the context of clinical trials (“coverage with evidence development”<sup>55</sup>). Currently, no large national payer reimburses for warfarin pharmacogenomic testing.

**Policy Recommendations**—We endorse the view of the SACGHS that “[T]he Centers for Medicare & Medicaid Services (CMS) should adopt a transparent, consistent, and evidence-based process for coverage, coding, billing, and payment of genetic tests under established benefits for testing. CMS processes should support patient access to accurate, reliable, and timely genomic testing; ensure continued investment and innovation in genetic and genomic technologies; reward value; account for rapid scientific and technical advances; and, most importantly, incentivize providers to use these important tools effectively to improve patient treatment outcomes.”<sup>56</sup>

Given the familial nature of genetic disease, one cannot consider the benefits or harms of genetic testing for an individual outside of the context of the larger family. Although insurance carriers are frequently shared among first-degree family members, coverage of extended families is usually distributed across multiple providers. We believe payers must work together for the benefit of these families and for the wider community and that such industry collaboration should be initiated by the payers themselves. Cost savings from reduced screening in those without the familial predisposition would release funds and provide an incentive for payers to establish an infrastructure for shared family care. In addition, current billing practice does not provide an adequate mechanism for reimbursement for screening at-risk relatives because it relies on the provision of a code that indicates an abnormal symptom or sign for the patient (and not the family).

## New Advances in Genetics and Genomics

### New Technologies

Advances in high-throughput sequencing offer unique opportunities, as well as significant challenges, for the future of genetic testing in CVD. New approaches have brought the cost of producing whole-exome or whole-genome sequences close to the current out-of-pocket cost of a focused panel reporting the exons of as few as 5 genes. However, at the time of this writing, whole-genome sequencing remains a predominantly academic exercise. Several companies have begun to offer direct-to-consumer (scientist or patient) whole-genome sequencing, which usually includes variant calling but little in the way of interpretation.

The challenges presented by the ability to cheaply sequence whole genomes are multiple. First, error remains a concern. At the present time, we recommend that clinical decisions be made only on the basis of variants verified with a secondary technique. Second, large areas of the genome remain especially difficult to sequence with short-read techniques (such as trinucleotide repeat regions). Third, genome assembly from short-read techniques is achieved by first mapping to the human reference sequence; however, at more than a million positions (depending on ethnicity), the haploid reference sequence is not the major allele. Indeed, at many positions, the “reference” allele has been shown to be associated with disease (for diabetes mellitus or factor V Leiden, for example). Thus, algorithms that call variants by first checking against the human reference may miss such calls. A “reference allele” human genome sequence would be a useful initial tool, although this is not without its own limitations, because it is possible that an allele that confers risk for one disease might be protective for another. Another approach would simply be to use the major allele at a given position, with the advantage that an ethnicity-specific reference could be used. A third approach is to use “alternate allele aware” assemblers. However, as technology evolves and longer-read techniques begin market penetration, *de novo* assembly will become routine, and overreliance on the current human reference (which contains the DNA of a pool of unknown individuals) will be avoided. Fourth, even after accurate sequence and variant calls can be made, the majority of the variants in any individual’s genome remain of unclear clinical significance. Large-scale studies of both normal and disease-causing genetic variation are needed to enable interpretation of whole-genome data. This will involve functional studies of variants, as well as segregation in kindreds. Fifth, although the test may be ordered to help define the cause of a specific disease, sequencing the whole genome could reveal information about risk for many other diseases, as well as demonstrate relatedness or lack of relatedness to other individuals (eg, nonpaternity) or groups (eg, ethnicity). Because no framework exists for the adequate interpretation of much of these data, counseling to deal with these specific issues is recommended before testing, or consideration of a focus limited to the areas of the genome relevant to the disease in question is warranted. Finally, although the cost of generating sequence continues to decline,

the cost of interpretation remains high. Despite this, the potential of whole-genome sequencing to impact medicine is highly significant.

### Biobanking

A number of institutions have made extensive commitments to support large-scale tools for discovery and implementation in personalized medicine. Elements include DNA repositories linked to disease-specific or disease-agnostic (eg, EMR-based) clinical records and investments in a range of key disciplines across translational science, genomics, and informatics that are required to exploit these resources. Some repositories also collect serum or tissue. The goal of discovery and replication of genotype-phenotype associations is further facilitated by NIH-supported alliances among these programs<sup>57</sup> that also encompass other stakeholders, such as the HMO Research Network and Pharmacy benefits companies. As these systems mature, they may also provide platforms for testing how best to implement a vision in which data on genetic variation are routinely incorporated into the clinical workflow.

The Vanderbilt University<sup>58,59</sup> and the Harvard Partners Crimson<sup>60,61</sup> programs use the model of capturing blood samples that have been obtained in the course of clinical care and linking these to deidentified EMRs. The deidentification step may allow this model to be implemented (after review by the institutional review board) without a consent form, although patient education material and opt-out mechanisms can be put in place.<sup>58,59</sup> This approach has the advantage of scale: As of May 2011, the Vanderbilt DNA repository, BioVU, contained samples from >120 000 patients. Another advantage is that by working in an EMR environment, the systems develop new informatics tools that may prove generically useful as genomic information accumulates in EMRs.<sup>60,62</sup> A disadvantage of this approach is that deidentification precludes any contact with the patient from whom the sample was collected, and thus, information not in the EMR is not available. This often includes key variables such as family history and detailed environmental exposures. Vanderbilt has also initiated a program to begin to preemptively embed genotypes judged to have clinical applicability into the EMR. The initial focus is on clopidogrel and CYP2C19 variants assayed in a CLIA-approved environment.

An alternative model is to prospectively obtain consent from each individual participating in a biobank. This allows recontact with the subject but is more expensive to implement. The largest such project is the British Biobank, which has collected bio-specimens and extensive phenotypic information from 500 000 middle-aged subjects; the plan includes linkage to EMRs over the next 3 to 5 years. The Northern California Kaiser biobank is also built on a consented model and includes >100 000 DNA samples extracted from saliva. Other sites using this approach include the Marshfield Clinic<sup>63</sup> and Northwestern University.<sup>64</sup>

### Privacy and Protection

Genetic exceptionalism is the idea that genetic information has inherently unique qualities that call for unique protections, and although many do not subscribe to this notion, some situations seem to argue for it. Examples include reidentification of deidentified data, derivation of genotype from genealogy sites (the tracing of an anonymous sperm donor by his offspring was one high profile example), identification of an individual through the DNA of a first-degree relative, and the inference of phenotypes such as hair color and eye color from genetic data.<sup>65</sup> The increasing availability of data in private or public databases along with developments in technology bring these issues to the fore. Although the NIH continues to endorse the concept of genetic privacy, and Title II of the Health Insurance Portability and Accountability Act (HIPAA) addresses the security and privacy of health data, others have suggested that complete genetic privacy cannot ever be guaranteed.

One of the most high-profile alternative models is that of open consent. In its first iteration, this invention of the Personal Genome Project allowed only for those with a Masters-level education in genetics to consent to enrollment (although enrollment has now been extended to several thousand individuals, and the entry criteria have been relaxed). The guiding principle is that research participants accept that no guarantees are given regarding anonymity, privacy, and confidentiality and that participation involves a certain risk of harm. Such models represent one response to the public availability of genetic data and to episodes such as the imputation of James Watson's apolipoprotein E haplotype status from surrounding SNPs, despite the fact that the alleles had been redacted.<sup>66</sup> Shortly after this publication, a much larger 2-Mb region was redacted.<sup>67</sup>

**Policy Recommendations**—Technological advances provide challenge and opportunity. In relation to the interpretation of whole-genome sequences, there is currently no unified database of human genetic variation that exists in a form that allows clinical application. Present National Center for Biotechnology Information comprehensive databases (eg, the Database of Genotypes and Phenotypes, known commonly as dbGaP) are encyclopedic in nature and lack the structure and level of detail that would allow application of findings to variant calls in individuals. We recommend a large investment in an infrastructure to catalog human genetic variation. Such an outlay would pay dividends in leveraging the significant investment of many funding bodies in generating the disease-association data. Participation in the contribution of variants from commercial genetic testing companies should be encouraged. In parallel, federal support for the infrastructure for large biobanks will allow the reach of genetic studies to extend to smaller populations and rare variants. Increased education of healthcare providers, patients, and their families is a key step to informing patients and thus maximizing the value of provider-patient partnerships that will define the future of CVD.

## Education of Health Professionals

New technologies will generate an enormous amount of patient-specific genetic and genomic information, much of which will be completely new to the practicing clinician. This will place a substantial burden on the individual practitioners, who will require ongoing education in a broad range of areas.<sup>68</sup> One of the earliest organizations to address the educational needs of health professionals was the National Coalition of Health Professional Education in Genetics. The organization was founded by the American Medical Association, the American Nurses Association, and the National Human Genome Research Institute in 1996 for the purpose of promoting genetic and genomic education among health professionals. Currently, the coalition consists of >100 health disciplines and health-related agencies and groups.

In response to the continuing learning needs of health professionals, the third edition of the “Core Competencies in Genetics for Health Professionals” was published in 2007. The document sets forth a set of 18 core competencies to guide the effective integration of genetics and genomic advances into practice and education across the professions. In addition, these competencies have served as a framework for development within specific disciplines. An example is the “Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indicators,” developed to guide the integration of genetic and genomic information and principles of care into nursing education and practice.

## Physician Education

Despite a crowded curriculum, medical students and physicians will require a much more detailed appreciation of the role of genetics in disease. This begins with a reemphasis on the taking of a family history: That a rigorous family history can take time; that for genetic



disease, obtaining a family history may be better viewed as a process, at times extending over multiple clinic visits; and that family history is dynamic (nonpenetrant disease may become clinically detectable in the future). In addition, clinicians will need to be familiar with different levels of genetic evidence and the potential confounders in studies that incorporate genetic data. It will be important to have a working knowledge of the basic principles of genotyping and sequencing methodologies and their technical limitations. Providers will also require skills in the interpretation of genetic test results in individuals, families, and populations. The downstream implications and follow-up investigation of genetic test results will require extensive educational support. Together, these educational goals will mandate a detailed understanding of fundamental genetic concepts that are currently underemphasized in the medical education of students and doctors.

An important topic for such educational programs will be the devolution of communication of the results of genetic testing. Although specialists are likely to continue to care for families with rare hereditary conditions and to perform risk assessments for many common diseases, as genetic and genomic information is more broadly applied, other members of an individual's care team will increasingly be called upon to integrate genetics into that individual's care, including primary care doctors, nurses, pharmacists, and specialist physicians such as cardiologists.

Furthermore, as the range of technologies expands, the educational mission may need to incorporate a basic understanding of large data sets, including whole-exome and whole-genome sequences, metabolomics, proteomics, and others. Providers will require instruction in the interactions between the patient genome and other genomes, especially the microbiome, as well as interactions with drugs, environment, and the epigenome. The integration of large data sets and their combination with existing clinical or functional information will require the development of novel tools to bring this information to the provider in a tractable form. The paradigms of clinical decision making are likely to change as old models of analysis are swamped by the volume of emerging data. The influence of family and individual data on our understanding of the role of genetics suggests that new actionable information may arise in close to real time (for example, segregation data from a family in one country may arise and immediately influence the interpretation of a genetic test in another). These challenges will mandate the reengineering of many aspects of the clinical decision-making and education interfaces. Education and clinical practice should move toward a single shared environment. Furthermore, remodeling of multidisciplinary care teams may occur with incorporation of genetic evaluation support personnel.

### Pharmacist Education

Pharmacists have the potential to play a particularly important role in the clinical implementation of pharmacogenomics information into practice. As experts in drug therapy, they are positioned to recognize the circumstances in which genetic information might most positively inform a therapeutic decision and to interpret the pharmacogenetic information once available. This potential role for pharmacists has long been recognized by the pharmacy academy, and in 2006, the Accreditation Council for Pharmacy Education, which accredits all colleges of pharmacy in the United States and Canada, adopted curricular standards that included incorporation of genetics and pharmacogenetics/pharmacogenomics into the curriculum. This means that all accredited colleges of pharmacy in the United States and Canada must provide evidence for meeting curricular standards (eg, in providing a stand-alone course) as they relate to genetics and pharmacogenomics. Such accreditation standards help to ensure that an increasing percentage of practicing pharmacists will have knowledge and expertise in this area, allowing them to serve as important members of the healthcare team and to incorporate genetic information into the optimal care of patients.

## Nurse Education

Several nursing organizations have endorsed the inclusion of genetic and genomic education in their curricula, including the American Association of Colleges of Nursing, the National League for Nursing, the American Nurses Association, and the Council on Cardiovascular Nursing of the American Heart Association. In addition, an emphasis on genetic and genomic education in the American Association of Colleges of Nurses education standards for baccalaureate and master programs reflects similar support.

Various approaches have been used to integrate genetic and genomic education into nursing curricula, ranging from inclusion of concepts into existing course lectures to the development of individual courses focused on genetics and genomics. As with health professions in general, however, limited genetic knowledge among nurse educators has presented a barrier. Several innovative programs have been initiated to address this, including Web-based faculty training modules, summer institutes for faculty development in genetics, and Master's programs in genetics that incorporate a focus on the educator role. An online tool has also been launched recently by the National Human Genome Research Institute. The Genetics/Genomics Competency Center is a Web-based repository of resources that support the integration of genetic and genomic education of nurses and physician assistants.

## Genetic Counselor Education

Genetic counselors are healthcare professionals who specialize in helping patients understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease. The demand for genetic counseling services is increasing with the increased availability and use of various types of genetic tests. Medicare and professional society guidelines often recommend that genetic testing for mendelian diseases be accompanied by genetic counseling. The number of individuals being assessed for hereditary diseases and predispositions is likely to increase as more genes associated with disease are uncovered with new, powerful, next-generation sequencing technologies and as more people have access to the sequence of their entire genome. An expansion of access to genetic counseling services will be a key component of realizing the benefits of these innovations.

Access to genetic counseling in general and to specialized genetic counseling in particular is limited by the number of genetic counselors and their geographic location. In the United States, there are currently 2200 board-certified genetic counselors with 32 Masters-level training programs graduating 400 students per year. Although the number of genetic counselors trained each year has been increasing steadily, more significant growth is needed. In a report to the SACGHS, the National Society of Genetic Counselors noted that the major barrier to increasing the size of the genetic counseling work force is a lack of sufficient funding for training programs. The National Society of Genetic Counselors recommended increased funding to help new programs to start and existing programs to expand, with consideration of training grants, similar to those used to fund doctoral and fellowship training.

With the introduction in 2007 of a *Current Procedural Terminology* code specific to genetic counseling services (96040), revenue generated via genetic counseling has increased, which in turn increases the number of genetic counseling positions that a given institution can fund. Access to genetic counseling services would be further improved by reimbursement policies that allow genetic counselors to bill Medicare directly and to bill for services provided outside the traditional face-to-face clinical model. Reimbursement for phone- and computer-

based services would also permit more individuals who do not live near a genetic counselor to access such services.

**Policy Recommendations**—Genetics and genomics should be included as a fundamental part of the training curriculum for all health professionals. Continuing medical education should be offered to current practitioners to facilitate knowledge in a rapidly advancing area. Programs for subspecialty education should be offered across the health professions. The training capacity for genetic counselors should be expanded.

## Conclusions

The rapid pace of advancement in genetic technology offers great promise in its potential to transform patient care. As a result, policies, systems, and processes designed for an earlier era of medicine will be forced to adapt. The American Heart Association is committed to the support of innovative research in cardiovascular genetics and its safe and efficient translation to patient care. In this report, we address the principal areas of challenge in the coming years. We have laid out a framework to guide policy makers in the way we believe will best support our patients, as well as the scientists and physicians focused on cardiovascular health around the world.

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## Disclosures

### Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all writing group members are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\* Modest.

<sup>†</sup> Significant.

## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest
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\* Modest.

Table

## Health Insurance Company Coverage Positions on Pharmacogenetic Testing for Clopidogrel and Warfarin

Company	Clopidogrel	Warfarin
Aetna	Aetna considers 1 genotyping for CYP2C19 polymorphisms medically necessary for persons who have been prescribed clopidogrel (Plavix). Repeat CYP2C19 genotyping has no proven value	Aetna considers genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system, including warfarin) experimental and investigational because the clinical value of this type of genetic testing has not been established Aetna considers genotyping for VKORC1 polymorphism (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the vitamin K epoxide reductase complex subunit 1 gene, including warfarin) experimental and investigational because the clinical value of this type of genetic testing has not been established
Blue Cross/Blue Shield	No mention	No mention
Cigna	No mention	Cigna does not cover pharmacogenetic testing for warfarin metabolism because it is considered experimental, investigational, or unproven. Effective date July 15, 2010
Group Health	No mention	The following technologies are considered investigational because of limited or no evidence to support clinical utility: Pharmacogenetic testing for medication sensitivity to any drug, including warfarin therapy
Guardian Life Insurance	No mention	No mention
HealthNet	No mention	No mention
Humana	Genetic testing offers great promise for treating or preventing certain conditions. Its proven relevance, however, is limited to certain diseases and treatments. For this reason, Humana does not cover home genetic testing kits or, at this time, pharmacogenetic testing	Genetic testing offers great promise for treating or preventing certain conditions. Its proven relevance, however, is limited to certain diseases and treatments. For this reason, Humana does not cover home genetic testing kits or, at this time, pharmacogenetic testing
Kaiser Permanente	No mention	No mention
Medica	Cytochrome P450 (CYP450) genotyping is investigative and therefore not covered	Genetic assay for warfarin response is investigative and therefore not covered
Oxford	No mention	No mention
Pacificare	No mention	No mention
Unicare	No mention	No mention