ANYONE WHO HAS BROWSED THE HUMAN GENOME SEQUENCE CAN READILY appreciate its immense power and potential as well as its staggering complexity, and imperfection. Nevertheless, following its release, British Prime Minister Tony Blair declared, “Today we are witnessing a revolution in medical science whose impact can far surpass the discovery of antibiotics.”1 And just 5 days prior, fears about the creation of a “genetic ghetto” swirled around London when one of Britain’s largest private life insurers to revealed that it had illegally used data from experimental genetic tests to evaluate some insurance applications.2 Could genetic research rival the clinical utility of antibiotics or spawned a genetic underclass? We do not yet know. Only gradually, through painstaking research, will the true social and medical impact of genetic science be clarified.

This issue of msJAMA explores how researchers, policy makers, and clinicians are defining a role for genetics in preventive medicine. One essential component will be determining the risk conferred by particular genotypes. Complicating this process is the fact that many diseases may have multiple genetic etiologies or may arise from complex interactions between several genetic variants and environmental factors. Karen Steinberg, Marta Gwinn, and Muin Khoury discuss the role of the Centers for Disease Control in dissecting the genetic etiologies of common diseases. Wendy Rubinstein and Reynold Lopez-Soler explore the heterogeneous genetic causes of sudden cardiac death. However, even the most comprehensive genetic databases cannot be useful without the means to integrate that information into clinical practice. Sue Goldie and April Levine discuss analytic methods used to evaluate the clinical utility and cost effectiveness of genetic testing. John Phillips presents important clinical tools that can facilitate the application of genetic information to patient care.

In examining the human genome project Freeman Dyson noted, “Technology only gives us tools. Human desires and institutions decide how we use them.”3 The use of poorly studied genetic tests to inflate insurance premiums, or fears that genetic research will result in genetic discrimination, constitute harmful reactions to incomplete data. Moreover, given the potential social and economic importance of genetic research, premature reactions to it will not be easily averted in the near future. In realizing the benefits of genetic testing in disease prevention, physicians and policy makers must establish mechanisms to evaluate and respond to the implications of new genetic information as soon as it becomes available. They can thereby protect the public, not only from disease, but also from alarmists and profiteers.

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Francis Collins and colleagues articulated a vision for using genomics in disease prevention in a “hypothetical case in 2010.” In this case, a 23-year-old man named John elects to undergo DNA testing for genes related to several diseases. The results suggest that while John is at lower than average risk for prostate cancer and Alzheimer disease, he is at increased risk for lung and colon cancer, as well as for coronary artery disease. Fortunately, preventive interventions are available to help John reduce his risk of developing each of these diseases. Making this hypothetical case scenario even remotely possible by 2010 will require a concerted public health effort to translate genomic sequence data into new opportunities for disease prevention.

The Genetics of Common Diseases

Traditionally, genetic diseases have been perceived as rare conditions resulting from high-penetrance mutations inherited in a Mendelian fashion such as Tay-Sachs disease. However, the etiology of common chronic diseases such as cancer, heart disease, and diabetes also has a significant genetic component. In these cases, inheritance is non-Mendelian and complex, making the causal genetic factors difficult to identify. Variants of multiple genes may each contribute a small part of the total risk for an individual. For example, evidence supports a role for common variants of a drug-metabolizing enzyme, N-acetyltransferase, in mediating susceptibility to sporadic bladder and colorectal cancer. Because these variants only become risk factors in the presence of bladder or colon carcinogens, they alter an individual’s risk only slightly, but they may be responsible for a large number of cancers in populations that are exposed to carcinogens.

Currently, because the presence of common genetic polymorphisms alone cannot accurately predict disease susceptibility, genetic tests for these variants rarely furnish information that can be used in prevention. The hope for the future is to learn what combination of gene variants and environmental factors predispose people to disease, and to use this information to prevent disease. For example, people who have the gene variant that codes for the “slow-acetylator” form of N-acetyltransferase, and who have a specific combination of other, as yet unidentified, risk factors, might be counseled to avoid working with bladder carcinogens like aniline dyes. In the future this model may provide targeted intervention and prevention. The US Centers for Disease Control and Prevention (CDC) has detailed the essential public health functions for genetics to play a role in disease prevention.

Public Health, Genetics, and Disease Prevention

Population based epidemiological studies are needed to learn the prevalence of gene variants that predispose people to disease, the burden of disease and death caused by these diseases, and the prevalence of disease-causing environmental exposures in genetically susceptible people. These studies are also needed to identify how environmental factors interact with genetic factors to cause disease. Such studies will often take years to complete, although in some cases, the information can be obtained retrospectively using incident case-control studies that are derived from population-based registries of diseases.

For genetic tests to have practical value, they must be evaluated for their sensitivity, specificity, and positive predictive values in relation to measured genotypes (analytic validity) and specific health outcomes (clinical validity). To calculate these essential parameters, information about the prevalence and penetrance of disease-associated gene variants is required from population-based studies. When this information is available, genetic tests may improve the clinical predictive values of traditional risk factors for disease. For example, hypercholesterolemia is an independent risk factor for heart disease that can be treated with statin drugs. Because nearly one third of the US population has hypercholesterolemia, an important public health priority would be to optimize the cost-effectiveness of statin therapy. Genetic testing may one day identify the population that will benefit most from these drugs.

As more genetic tests are developed and marketed, it will be important to evaluate the value they add to existing medical and behavioral interventions. Population research will facilitate this evaluation of genetic testing and thereby prevent its misuse while helping to realize its benefits. Although new developments in genomic medicine will give physicians new tools for promoting health, preventing disease, and managing illness, they will also create a new responsibility to ensure they are used wisely and well.

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Sudden Cardiac Death (SCD) is a widespread health problem with several known genetic etiologies. SCD generally occurs in healthy individuals who do not have other conventional cardiac risk factors. A parental history of SCD carries a high relative risk of SCD, suggesting an independent pathway with a genetic component.

William Bateson, the “father of genetics” who translated and revived Mendel’s works, advised, “treasure your exceptions.” Along these lines, studies of relatively rare genetic disorders of the heart can provide a guide to the numerous genetic etiologies of SCD, which may be important in the general population. For example, the synchronized ionic cascades of the cardiac action potential are manifested in disease by the ion channelopathies. These include congenital long QT syndrome (LQTS) which causes prolongation of the QT interval resulting in syncope, seizures or sudden death. One form of LQTS, caused by disruption of the KvLQT1 gene, is exacerbated by exercise whereas SCN5A sodium channel gene mutations are typically associated with arrhythmias at rest. Carriers of KvLQT1 mutations respond to β blockers and avoidance of adrenergic stimuli, while those with SCN5A mutations are exorted to undergo placement of implantable cardioverter defibrillators since their arrhythmic events are more lethal. Thus, disease management can be informed by an understanding of genetic pathophysiology.

Malignant ventricular arrhythmias leading to SCD are a major final common pathway in myocardial ischemia and infarction, as well as in congestive, hypertrophic, and dilated cardiomyopathies. Most cases of SCD are not associated with well-characterized genetic syndromes such as LQTS. Therefore, it is often assumed that genetic mutations of SCD loci have little public health significance. However, prolongation of the QT interval during the first week of life is strongly associated with sudden infant death syndrome, perhaps caused by de novo mutations in LQTS genes. Moreover, drug-induced QT prolongation has been reported in patients with otherwise silent LQTS mutations. There could be considerable public health benefits if genetic variants for SCD were considered in the differential diagnosis for drug-induced QT prolongation, syncope, seizures, unexplained drowning, and sudden death.

It is therefore important to study allelic variation in the numerous genes involved in the rare hereditary SCD syndromes in patients with several different cardiac diseases. Subtle genetic disruptions in these genes may be responsible for more common forms of SCD. For example, several single nucleotide polymorphisms (SNPs)—changes occurring in at least 1% of the population—have been identified in genes which, when dysfunctional, cause hereditary arrhythmias and cardiomyopathies. Some of these variants may be benign, but others, either alone or in certain combinations, may lead to functional changes in the action potential, force generation, and membrane stability. It is now feasible to compare the prevalence of numerous SNPs in affected versus healthy individuals using high throughput genotyping technology. Although the genetic etiology of disease or pharmacological response may be quite complex, statistical methodologies have been developed for correlating clinical phenotype with groups of interacting genes and environmental exposures.

Genetic testing for hereditary SCD is challenging due to the need to examine multiple causative genes with numerous potential mutations, but the benefits could be great. Pinpointing the genetic cause makes subsequent intrafamilial testing highly sensitive and specific, and relatively inexpensive. SCD may be prevented in relatives by lifestyle changes and medical intervention, and noncarriers and their children can be relieved of the medical and psychological burdens of being susceptible to SCD. In addition, genetic profiles contributing to common forms of SCD may reveal more continuous degrees of risk than the all-or-nothing phenotype in LQTS but should provide a plethora of strategies for rational drug therapies and prevention.

The ultimate promise of molecular medicine is to unlock the passageways to targeted therapy. If genetic etiology plays an important role in SCD due to common heart disease, SIDS, and drug-induced QT prolongation, then genetic screening will substantially improve the medical management of these diseases. Increasing evidence of an enormous degree of allelic variation between individuals supports a prevailing theory that many different alleles collectively contribute to common diseases. It is now possible to begin deciphering this complexity by using the clues of classical clinical genetics and the tools of modern molecular genetics.

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Genetic testing has many promising applications, including the possibilities of assessing predisposition to disease and predicting drug efficacy or toxicity in individuals with specific genetic profiles. Determining how best to use these technologies will require consideration of the clinical benefits and costs, both to individuals and to society. Cost-effectiveness analysis is increasingly being used to weigh these factors and thus to determine the relative value of new technologies.

The fundamental principle of cost-effectiveness analysis is that choices must be made between alternative uses of limited resources. A cost-effectiveness analysis can illustrate the relationship between the net resources used and the net health benefits gained for a specific clinical intervention (such as genetic testing) compared with an alternative (such as phenotypic testing). It can illustrate the tradeoffs with different policy choices and can provide quantitative insight into the relative importance of different parameters, thus helping to determine which variables are most important to measure in clinical research.

Genetic tests will generally be used to identify susceptibility to disease or to a certain type of drug response, rather than to confirm the presence of disease. The cost-effectiveness of genetic testing will depend on the value of this information to patients and to society. Susceptibility is determined by the risk of disease among gene carriers (i.e., gene penetrance), which may vary substantially between high-risk families and the general population. Therefore, the most critical parameters in cost-effectiveness analyses of genetic testing will be the target population, the prevalence of the mutation, and gene penetrance.

Genetic tests for the detection of variant genes are typically very accurate for the detection of the presence or absence of a mutation. For example, consider a woman identified with a BRCA-1 mutation, which is associated with familial breast cancer. If she has the mutation, the probability of a positive test result is close to 100% (i.e., sensitivity of 1.0). However, the appropriate measures of sensitivity and specificity for use in a cost-effectiveness analysis—the clinically meaningful test characteristics—should reflect the degree of association between the genotype and the clinical phenotype. For a cost-effectiveness analysis to be useful in informing policy, it should consider all clinical and economic events triggered by the positive test result. For a woman who tests positive for the BRCA-1 mutation but is not destined to develop breast cancer, the benefits of a prophylactic mastectomy would be negligible but she would still bear the huge costs of the psychological anxiety and health care resources associated with lifelong screening. From the perspective of a genetic screening program, this should be considered a “false-positive” result.

A genetic testing strategy is more likely to be cost-effective when the genotype and clinical phenotype are tightly linked, when the next best alternative is less effective or more costly, and when there is an effective intervention that can be implemented on the basis of the genetic information. It is less likely to be cost-effective when penetrance is incomplete, when effective alternative tests exist, and when there is no treatment for the disease. We will describe several specific aspects of cost-effectiveness analysis that are particularly relevant to genetic screening.

Study Perspective and Time Horizon

The perspective of a cost-effectiveness analysis dictates which costs and which health benefits should be counted. For studies that affect the broad allocation of health care resources, a societal perspective is recommended. This means that all costs and all health effects should be incorporated regardless of who incurs the costs and who obtains the clinical benefits. This is particularly relevant for genetic testing because unlike other medical tests, genetic tests reveal information not only about patients but also about their relatives. For example, in addition to direct medical costs borne by the patient, a cost-effectiveness analysis of BRCA-1 testing should include costs related to any consequences (e.g., psychological harms) experienced by family members. Analyses that adopt other perspectives are no less valid, but serve different goals. For instance, from the patient’s perspective, the most relevant costs might include the future medical costs borne out of pocket due to loss of health insurance.

The time horizon of an analysis should also be long enough to incorporate all relevant future effects of an intervention. In most cases, modeling will be required to extend the analysis beyond the original time frame of the primary data to estimate longer-term outcomes. Thus, there will be inevitable assumptions with respect to data extrapolation and imputation. For example, data may be available for the prevalence of a genetic variant and the corresponding risk of cancer in the gene carrier. To estimate life expectancy, the analysis would need to combine data on cancer incidence, treatment efficacy, and the probability of survival conditional on the stage of disease. This process will involve the specification of survival parameters, the choice of disease-specific or total mortality data, and the decision to represent certain event probabilities as conditional upon patient characteristics, such as age, sex, risk factors, stage of disease, and prior morbidity. The implications of these assumptions are substantial.
sumptions will need to be explicitly described when reporting cost-effectiveness results.

Health and Economic Outcomes

Genetic testing may affect a person’s health-related quality of life in both positive and negative ways. For example, there are emotions aroused by learning that one is—or is not—likely to develop a serious disease, and reliable methods to measure this psychological impact are still needed. The usual approach to incorporate both the prolongation and quality of life in cost-effectiveness analyses is to express clinical benefits in terms of quality-adjusted life years (QALYs). QALYs represent the benefit of a health intervention in terms of time in a series of health states, which are assigned a weight that reflects the desirability of living in the state, typically from “perfect” health (weighted 1.0) to dead (weighted 0.0). Once the quality weights are obtained for each state, they are multiplied by the time spent in the state; these products are summed to obtain the total number of QALYs. These quality weights reflect the fact that people with similar abilities to function, or in similar current health, may value that level of health differently. For example, 2 individuals with identical health status and the same variant of the familial adenomatous polyposis gene might very well perceive colectomy differently and thereby place different quality weights on this health state. Thus, even if they faced identical life expectancies their quality-adjusted life expectancies would differ by virtue of their individual preferences.

While measures of health outcomes are included in the denominator of the cost-effectiveness ratio, all relevant costs related to the intervention itself (e.g., counseling) and the downstream events triggered by different test results (e.g., screening) should be included in the numerator. These include direct health care costs (e.g., testing, medication, procedures), direct non-health care costs (e.g., transportation costs for clinic appointments), and patient time costs. Other costs likely to be important in the context of genetic testing include those needed for public health education efforts, training of genetic counselors, privacy safeguards in health-care settings, and anticipated litigation.

While a genetic test may be costly, the long-term consequences may make it an efficient use of resources (i.e., cost-effective). For example, genotyping can detect mutations associated with resistance to antiretroviral drugs for HIV. This information can then be used to optimize the choice of antiretroviral therapy. Although the test costs more than $500, genotyping for resistant mutations has been found to be cost-effective. Thus, the incremental price of obtaining a unit health effect (usually dollars per QALY) as a result of a given clinical intervention when compared to the next best alternative. Because cost-effectiveness analyses are always incremental, the intervention of interest (e.g., genetic testing) must be compared to all reasonable alternative strategies. If all relevant options are not included, there is a risk that genetic testing will erroneously be found to be cost-effective. For example, an analysis to evaluate the cost-effectiveness of detecting cytochrome P450 mutations (which are associated with poor metabolism of warfarin) would need to assess the additional costs and benefits of genotyping compared with the relevant phenotypic test (e.g., routine monitoring of the international standardized ratio).

The uncertainty in a cost-effectiveness analysis is evaluated by sensitivity analysis, which involves testing the stability of the conclusions over a range of parameter estimates and structural assumptions. In the context of genetic testing, special attention should be paid to understanding the implications of varying parameters governing the frequency and severity of the clinical and economic consequences of the disease, the phenotypic expression of genetic variation, and the genetic test characteristics.

Advances in genetic science will undoubtedly influence clinical medicine, public health, and health policy. Developing sound policy for questions related to genetic testing must take into account issues wider than the health of the patient because the consequences extend to other related individuals, as well as to society at large. As a result of the pace at which specific genes are being implicated in disease processes and drug metabolism, there is a risk that genetic testing policy could be made prematurely. It is important to ensure that clinical recommendations do not outpace the rate at which the effectiveness, the balance between risks and benefits, and the cost-effectiveness of genetic testing can be rigorously evaluated.

Results of a Cost-Effectiveness Analysis

The results of a cost-effectiveness analysis are summarized using an incremental cost-effectiveness ratio, which represents the incremental price of obtaining a unit health effect (usually dollars per QALY) as a result of a given clinical intervention when compared to the next best alternative. Because cost-effectiveness analyses are always incremental, the intervention of interest (e.g., genetic testing) must be compared to all reasonable alternative strategies. If all relevant options are not included, there is a risk that genetic testing will erroneously be found to be cost-effective. For example, an analysis to evaluate the cost-effectiveness of detecting cytochrome P450 mutations (which are associated with poor metabolism of warfarin) would need to assess the additional costs and benefits of genotyping compared with the relevant phenotypic test (e.g., routine monitoring of the international standardized ratio).

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The goals of genomic medicine are to provide early detection of genetic predisposition by appropriate testing, and to offer individualized treatment. Increasingly, genomic medicine may address common conditions known to have significant genetic components, such as hypertension, obesity, diabetes, cancer, and affective disorders. Early treatment could then be used to prevent or ameliorate some diseases, while prenatal counseling would be appropriate for diseases that are lethal, severely disabling, or cannot be treated. To optimize identification of genetic diseases and risk factors, physicians must synergistically use information about the patient's signs and symptoms, his or her family medical history, and knowledge of the genetic etiology of disease.

Recognizing Genetic Diseases
Knowledge of the patient’s family medical history can play an important role in the initial detection of genetic diseases. Ideally, such histories include information about which genetic diseases have occurred in the patient, as well as in their parents, siblings, children and other relatives. From these histories risk factors can be identified to determine more accurate estimates of recurrence and predisposition.

Because of the rapid rate at which genetic bases of human diseases are being discovered, there is no printed reference that can provide current information about all the clinical and laboratory findings consistent with genetic disease, or which laboratories perform specific genetic tests. Increasingly, electronic databases are becoming an important source for this information because they are easy to update and can be searched interactively. For example, imagine that you are asked to see a 16-year-old girl with the following clinical characteristics: height greater than 95 percentile, dislocated lens, pectus excavatum, and joint hypermobility. Her father died of a ruptured aortic aneurysm at age 42 years. To generate a differential diagnosis you perform a keyword search of the Online Mendelian Inheritance in Man (OMIM) database which contains information on more than 12,800 genes or genetic disorders. When you search for entries containing the 5 search terms terms, “tall stature,” “dislocated lens,” “pectus excavatum,” “joint hypermobility,” the database returns only 2 OMIM entries. The first states that Fibrillin mutations are the major cause of Marfan syndrome (MFS). The second states that MFS is an autosomal dominant disorder and it includes a clinical synopsis of associated physical findings, a “Clinical Features” section, and information on the diagnosis and clinical management of MFS. Importantly, this entry alerts you to the risk of aortic root dilation and the efficacy of β-adrenergic blockade in treating this complication of MFS.

More detailed information on the signs, symptoms, diagnosis and treatment of MFS and other genetic disorders can be found in the GeneClinics database. This also contains the addresses, telephone, and fax numbers of several laboratories that provide molecular testing for MFS in the GeneTests database. This database also provides contact information for genetic clinics throughout the United States. Finally, you can find information on insurance issues and support groups for patients and their families at the Genetic Alliance web site. Using these databases, you have generated a working diagnosis (MFS), obtained information about its pathogenesis, mode of inheritance, diagnostic criteria and treatment, found laboratories that can provide testing, and identified support and information sources for affected individuals and families.

Increasing Awareness of Research
Further improvement of genetic diagnostic methods and treatments will require that patients and their families participate in research efforts. Such studies can utilize linkage analysis, allele sharing, or association methods to identify genes that predispose to, or provide resistance to genetic diseases. Linkage analysis determines if selected genes co-segregate with a disease. They require DNA samples from patients and members of their families. Allele sharing studies determine if selected genes are found more often in siblings who share a disease, and thus predispose those with the gene to the disease. These studies only require DNA from affected siblings. Association studies determine whether selected mutations, which may predispose to or protect against disease, occur more frequently in affected patients or a control group. Association studies require DNA from affected but unrelated patients, and from control subjects from the same population.

Elucidating and managing the immense complexity of human genetic diseases is critical to the clinical application of genetic information. Taking a careful family history and using centralized databases on the Internet are powerful and straightforward ways to identify genetic diseases. As these databases grow they will also provide more comprehensive access to treatments, specialized laboratory tests and educational materials for patients and their families. Physicians should also help patients and their families become more aware of their own risks for genetic diseases and the potential to participate in research to discover better prevention and treatment for these diseases.

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