GENES AND DISEASES:

THE PHYSICIAN’S RECONCILING ROLE
The Human Genome Project (HGP) is methodically unraveling and extracting information from the DNA strands that constitute our genetic inheritance. One scientific endeavor to receive a boost from these data is the discovery of genes that are implicated in diseases. Identification of a gene permits the development of diagnostic tests that can reveal aberrations prior to manifestation of clinical symptoms. However, in many cases, medical treatment becomes scarce after a positive diagnosis has been made. We know, for instance, that Huntington disease is caused by expanded trinucleotide repeats in the huntingtin gene, yet no cures for the disease exist. What should be done in such circumstances?

We posed this question in the 1998 John Conley Ethics Essay Contest, in which medical students were asked to respond to this scenario: “Suppose you have a test that indicates a predisposition to a certain disease for which there is no treatment at the present time. How would you advise the patient?” Of the 63 submissions we received, no one claimed to have an absolute directive in this matter. Rather, they argued for an evaluation of each situation taking into account a differential array of social, technical, and economic factors.

A recurring issue in these essays concerned the uncertain legal protection patients have regarding their genetic information: how does predisposition to disease affect one’s ability to obtain employment or insurance? Another theme was the questionable usefulness of knowledge would have on the patient’s psyche. The room for error inherent in a diagnostic test and in translating concepts of probability into quality patient care were additional concerns raised. Perhaps the most surprising sentiment presented in these essays was the need for physicians and patients to accept their limitations. Students urged patients to give careful thought to coming to terms with their genetic makeup and physicians to realize the limitations of health care technologies. A sensitive but thorough grasp of what can be revealed through a predictive test, followed by a similar assessment of treatment options, appeared to be a viable solution to the question posed in our contest.

For now, this even-handed but ultimately unfulfilling answer may be the only course of action available for certain diseases. However, physicians and patients should take heart in the many proactive measures stemming from HGP advances. Powerful but unrefined tools such as gene therapy or pharmacogenomics are being developed to address genetic diseases. Perhaps these treatments will become standard remedies that obviate the scenario the contest presented. These treatments also raise new quandaries about altering an individual’s genetic heritage—ostensibly to cure diseases, but inevitably to effect more cosmetic changes. Whether this situation materializes in the future remains to be seen, but perhaps in 2003, when the HGP has completed its task, a future John Conley Ethics Essay contest will again explore the ethical use of genetic information. This time, the question may be: “What responsibility do physicians have in modifying a patient’s genetic heritage?”

References
Genetics in the Context of Medical Practice

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The Human Genome Project (HGP) is an international scientific effort to map and sequence the entire human genome. Since its inception in the United States in 1990,1,2 as a joint effort by the National Institutes of Health (NIH) and Department of Energy (DOE), the HGP now includes contributions from genome centers in the United Kingdom, France, Canada, Germany, and Japan. In September 1998, the NIH and DOE announced an accelerated timetable for sequencing the genome, and the entire human sequence is expected to be completed by the end of 2003.3 This information will benefit clinical medicine by enabling physicians to diagnose and treat heritable disorders more effectively.

From Maps to Medicine

Information from the HGP has accelerated the rate of gene discovery. Once a disease gene is identified, DNA-based diagnostic tests can be developed to detect at-risk individuals. Knowledge of a patient’s genetic makeup can allow physicians to minimize disease risk through preventive medicine and conventional drug therapies.4 A more novel treatment is gene therapy, which compensates for the defective gene by providing an exogenous functional copy. Another promising tool is pharmacogenomics, where a person’s genotype is used to predict those pharmaceuticals that will prove most therapeutic and identify those that could be deleterious. For example, the cholinesterase inhibitor tacrine appears to be less effective in Alzheimer disease patients who carry the apolipoprotein E4 allele.5

Defining the Role of the Primary Care Physician

As discoveries from the HGP are translated into meaningful medical diagnostics and therapeutics, genetics will heavily influence clinical decision making. As the number of treatable genetic diseases increases, physicians will need to use and interpret genetic tests correctly, determine those genetic treatments that are available, and learn how to access these services. Perhaps the most important role for the primary care physician is first to identify a potential genetic disorder. Hence, physicians must be prepared to integrate information derived from a careful family history with the molecular data provided by the HGP.

Genetics Education for Physicians

A recent American Medical Association (AMA) survey indicated that 59% of Americans are somewhat or very likely to take advantage of genetic testing and that 72% believe that their primary care physician can interpret these results.6 However, in a recent study, physicians misinterpreted nearly one third of predictive test results for colon cancer, and fewer than 20% of patients received appropriate genetic counseling.7 To strengthen genetics knowledge among physicians, recent guidelines by the American Society of Human Genetics have concentrated on increasing the emphasis on genetics in medical school curricula.8 To ensure quality continuing genetics education for health care professionals, the National Coalition for Health Professional Education in Genetics was developed in 1996 by the AMA, the American Nurses Association, and the NHGRI to provide genetics information online, better represent genetics on licensing examinations, and facilitate the development of core curricula in genetics.9

On the Safe Use of Genetic Tests

In 1997, the NIH-DOE Task Force on Genetic Testing issued a set of recommendations to ensure the safety and proper use of genetic tests prior to their use in a clinical setting.10 Recommendations include to (1) establish an Advisory Committee on Genetic Testing in the Office of the Secretary of Health and Human Services (HHS); (2) establish a means for prioritizing genetic tests in high- and low-scrutiny categories; (3) require that diagnostic labs setting up a genetic test design an institutional review board–approved protocol for collecting data on analytic and clinical validity; (4) recommend external review of protocol outcomes prior to marketing; (5) emphasize the need for public and professional education; and (6) emphasize the need for special consideration for testing rare diseases. Based on this report, the federal Advisory Committee on Genetic Testing, which will report to the HHS Secretary, was chartered in August 1998.11

Protecting Patient Rights

A recent survey indicated that nearly 7 out of 10 Americans are somewhat or very concerned that genetic information may be used against them by either their employer or health insurance provider.6 In 1995, a set of recommendations to lawmakers dealing with issues pertaining to health insurance and genetic discrimination was compiled by the NIH-DOE Working Group on Ethical, Legal and Social Implications of Human Genome Research and the National Action Plan on Breast Cancer.12 These guidelines would prohibit insurance providers from increasing premiums or determining eligibility based on predictive genetic information and would prohibit insurance providers from accessing or disclosing genetic information. A major step in this direction came in 1996 with passage of the Health Insurance Portability and Accountability Act (HIPAA), which prevents establishing in group health plans differential premiums based on genetic status and does not consider genetic information a “pre-existing” condition.13 Unfortunately,
the HIPAA does not ensure the privacy of genetic information, nor does it protect those insured in the individual market. Several active efforts are under way at the federal level to address these problems. The Patients' Bill of Rights Act, introduced by Republican members of the Senate in July 1998, would extend protection to those seeking individual insurance coverage by preventing the use of predictive genetic information to deny coverage. It would also protect policy holders and applicants from being forced to take genetic tests or provide the results of previous tests, and extends the definition of genetic information to include family history in addition to test results. While the status of this legislation is uncertain, it is clear that patients need to be protected from potential genetic discrimination and stigmatization, in both the health insurance and employment arenas.

Genetic technologies are increasingly relevant to both the diagnosis and therapy of human disease. If patients are to benefit from this knowledge, clinicians will need to incorporate genetic medicine into clinical practice much like any other aspect of the classic history and physical examination. Public interest in genetic advances, coupled with an explosion of information provided by the HGP, will place the primary care physician in a central role to deliver genetic discoveries to the patient's bedside. This truly is an exciting time to be practicing medicine.

1999 John Conley Ethics Essay Contest for Medical Students

The Medical Student JAMA is pleased to announce its fifth annual essay competition for medical students, sponsored by the John Conley Foundation for Ethics and Philosophy in Medicine. This year's topic examines an issue raised by the growing importance of cost containment in medical practice. Traditionally, optimal patient care has been the foremost concern of medicine. More recently, physicians are facing pressures to restrain health care expenditures, presumably without sacrificing the interests of the patient. In their essays, medical students are asked to address the following scenario: Suppose a potentially useful procedure is available that is not covered by a patient's medical insurance. Under what circumstances, if any, would you consider it appropriate to miscode (and thereby make available) the needed procedure?

Essays will be judged based on clarity of presentation and writing and applicability to actual decision-making. The author(s) of the best essay(s) will be awarded $5000 or a portion thereof and will be encouraged to use some of the funds to attend an ethics conference of their choice. Winning essays will be considered for publication in MS/JAMA. Essays must not have been previously published in print or electronic format and must not have been submitted to any other journal during the review period.

All current medical students are eligible. Essays should be less than 2000 words in length. Please submit essays typed and double-spaced, with the author's identification (name, address, telephone number, and medical school class) on a cover sheet only—not on the essay pages, which will be anonymously judged. Entries must be postmarked by January 15, 1999, and sent to: John Conley Essay Contest c/o MS/JAMA 515 N State St Chicago, IL 60610

References

The words of the prophet Tiresias have been quoted by more than one geneticist attempting to capture the dilemma that arises when prophecy precedes cure. Tiresias challenges the value of foresight, given an impending disaster that cannot be averted. Shaw, in contrast, shows how knowledge can be elevated to the status of an unconditional right. How, then, should we advise the patient who inquires about a test that identifies a predisposition to a disease for which there is no definitive treatment? This patient encounter is hardly a hypothetical one. Genetic tests that detect risk for conditions with familial components, such as Alzheimer disease, certain cancers, and even heart disease, have been the subject of much public and scientific discussion, not to mention commercial interest.

A test of this kind brings the patient to a crossroads at which he or she must confront a host of perplexing questions. Few susceptibility tests now available target a disease for which preventive or curative measures exist. Complicating the picture is the fact that these tests provide a suspicion of disease rather than a clear-cut prediction. Moreover, the predictive value of these tests may be heavily influenced by the population under study. It may be some time before routine testing in the general population for genes such as ApoE for Alzheimer disease or BRCA1 for breast cancer can be justified.

How should we address our patients’ concerns about their risk status? A medical anthropologist once observed, “The very cognitive mastery that clinicians possess exposes them to the futility of intervention.” Physicians may be tempted simply to dissuade patients who want to undergo testing or, alternatively, to concede to patients’ wishes with little discussion. Both temptations are very real in the world of the 10-minute visit and quick turnaround; but to give way to these impulses is a grave mistake. Even if we can refer such patients to an expert, it remains our responsibility to know what options are available. In this essay, I offer some thoughts on how we can exercise this responsibility.

What It Means to Know

A fundamental task for the patient and the physician when considering genetic susceptibility testing is to determine what significance the genetic information holds for all involved parties. In its newsletter, The Marker, the Huntington Disease Society of America invited at-risk individuals to share their thoughts and feelings on predictive testing. A recurrent theme in these accounts was the intensely personal and far-reaching nature of genetic information. Many individuals commented that genetic information exposed something basic and intrinsic about their identity. Some spoke of the discovery of an immutable flaw and the burden of a tarnished self-image.

Nonetheless, many people desire genetic information, even after they are made to understand its enormity. In families with Huntington disease, individuals are often painfully aware of their risk, having lived for years with mixed hope and dread. Genetic counselors have found that many people feel paralyzed by their risk status and, as a consequence, have difficulty moving in any purposeful direction. The patient’s decision to undergo testing often reflects a desire to move forward in some way, and to end a long-standing struggle with anxiety and uncertainty.

Foreknowledge about disease affords individuals time to strengthen support systems and reshape personal goals. This knowledge can guide plans regarding childbearing and careers. It can teach people to let go of the trivial things that threaten to spoil a moment and empower them to take action prior to the onset of illness. These measures may include joining a support group and moving closer to family or, alternatively, finding a one-story home and making appropriate financial arrangements. A discussion about end-of-life options might be initiated, if it has not already begun.

Choosing Not to Know

Physicians need to recognize that not all patients want to know their risk status, and many may be ambivalent about pursuing susceptibility testing. In a survey of individuals at risk for Huntington disease, 15.5% of the sample reported that they would not want to take the predictive test; 19.4% were simply not sure. These percentages may be even greater for susceptibility testing. We should remind patients that they can decline testing. Our respect for one patient’s decision to forego testing should match our respect for another’s desire to pursue it.

Susceptibility testing may have considerable psychological repercussions. Studies among women who have received cancer risk information suggest that test results have a profound emotional impact. The trauma of learning that one has the gene for an untreatable disorder may be even greater. One study suggested that about 2% to 6% of persons at risk for Huntington disease may have severe psychiatric or suicidal responses to a positive test result. Even recipients of a negative result may be haunted by "survivor guilt" on learning that they have eluded a disease that has taken others in their family.

Genetic test results do not always afford individuals the peace of mind they seek. The question of whether they will
Making. In light of these possibilities, confidentiality possibilities have held considerable influence in decision uncertainty. It is therefore essential that physicians present can, in turn, give a false impression of accuracy and cer-
ing the patient's choices. Numerical expressions of risk are not necessarily understandable to the anxious patient. The sensitivity, specificity, and positive predictive value of risk reduction behaviors are all complex concepts that must also be addressed.

The social repercussions of testing also warrant careful evaluation. For example, patients' insurance coverage may be jeopardized by genetic testing. Employment discrimi-

nation is another concern. It has been shown that employers are less likely to hire individuals with a personal or family history of medical problems. While there are few data on the extent of these risks to patients, these possibilities have held considerable influence in decision making. In light of these possibilities, confidentiality must also be addressed.

This process of educating patients has many subtleties. The sensitivity, specificity, and positive predictive value of a test; the penetrance of a given gene; and the efficacy of risk reduction behaviors are all complex concepts that are not necessarily understandable to the anxious patient. The language of risk itself poses challenges. The term predisposition is extraordinarily slippery. Predisposed does not mean predestined. Genetic counselors may try to avoid words such as "higher" or "unlikely" for fear of influenc-
ing the patient's choices. Numerical expressions of risk can, in turn, give a false impression of accuracy and cer-


tainty. It is therefore essential that physicians present information in a manner appropriate to the patient's level of understanding.

Final Thoughts

Too often, the patient's role in decision making is undermined by the hurried nature of medicine. I have heard the assertion "I've consented the patient" uttered as though informed consent were something to be foisted upon the patient. Ideally, informed consent and follow-up counseling should be an ongoing dialogue between patient and physician—wherein the patient participates as an active subject and not simply as a receptacle for information. The decision to undergo testing ultimately resides with the patient—we cannot lose sight of this simple fact.

Neither Tiresias' despairing pessimism nor Shaw's unconditional right-to-know provides an adequate framework for approaching the patient in question. The ideal physician is a skilled teacher who balances thought-
ful guidance with careful attention to the patient's indi-

vidual needs. It is inappropriate for us to impose our personal values on our patients, and it is equally unac-
ceptable for us to dispense information indiscriminately, only to sit back in silence as patients agonize, alone, over a final decision. Our fundamental challenge, as physicians entering the era of molecular medicine, is to tem-

per our newfound wisdom with an open-minded apprec-

iation of the unique needs of each individual we serve.

References

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Applications to join the 1999-2000 MS/JAMA editors group are now available through the AMA Division of Medical Student Services (DMSS) at (800) 262-3211 ext 4746 or on the MSS Web site (http://www.ama-assn.org/mss). Qualified medical students with diverse experiences and interests in writing, health care policy, multimedia publishing, poetry, and/or art are especially encouraged to apply. Applications must be received by the DMSS no later than January 15, 1999.

Winning and other selected essays are available on the MS/JAMA Web site at http://www.ama-assn.org/msjama.

MS/JAMA congratulates the 3 winners of the 1998 John Conley Essay Contest: Hyang Nina Kim, University of California San Francisco School of Medicine; Valerie A. Jones, Columbia University College of Physicians and Surgeons; and Warren Kinghorn, Harvard Medical School. We also wish to thank this year’s judges: Dr Arthur Caplan, Center for Bioethics, University of Pennsylvania; Dr Pilar Ossorio, Institute for Ethics, American Medical Association; and Dr Roger Rosenberg, Editor, Archives of Neurology.

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Mr Smith shifts uncomfortably in his imitation leather seat. He glances at the other faces in the dimly lit waiting room, each bearing an expression of personal anguish. A nurse ushers Mr Smith into an examination room. Minutes later, there’s a brisk knock on the door.

“Mr Smith?”

Mr Smith gazes up as the physician enters the tiny, sterile room. She shakes Mr Smith’s hand with both of hers. Mr Smith notes a worn, gold “Humanism in Medicine” badge pinned to her lab coat.

“What can I do for you today?” inquires the doctor, her eyes fixed on Mr Smith’s tense face.

“Well,” says Mr Smith, working hard to collect his thoughts, “my mother died two weeks ago . . . she died of Alzheimer’s. She was sick for a very long time. She seemed to deteriorate rather slowly. It was so hard on all of us. But that is not really why I am here. You see, I was reading about a new test that can tell whether a family member is at risk for developing Alzheimer’s, and I thought I’d better take it. I have three kids and a loving wife and I worry about their future. I don’t want them to go through what I did with my mom. She started getting ill when she was only 40. I have been really forgetful lately and I’m worried that I may have Alzheimer’s, too. What should I do, Doctor?”

Within the last few decades, rapid advances in genetic technology have outstripped developments in medical therapy. While researchers are able to identify genetic predispositions to a growing number of disorders, such as Alzheimer and Huntington diseases, little can be done to treat patients found to be at risk. This disparity between ability to detect and ability to cure gives rise to a multitude of ethical issues. In considering whether or not to recommend that a patient undergo genetic susceptibility testing, the physician should examine legal and confidentiality issues, possible psychological repercussions, financial constraints, implications for insurability, and technical limitations associated with the test.

Legal and Confidentiality Issues

The legal implications of predispositional genetic testing are far reaching. Issues ranging from disclosure of test results to the ethical use and handling of biological samples are subject to legal scrutiny. Does the physician have legal duties regarding disclosure of the test results to family members? What constitutes adequate informed consent and follow-up counseling? Can a physician be found liable for not providing a test that might have allowed a patient to anticipate the onset of disease? To what extent is a physician responsible for a patient’s maladaptive response to a positive test result?

Clearly, there are innumerable legal pitfalls associated with predictive genetic testing. However, many of them can be avoided if a sensitive, confidential, and preapproved protocol is followed. Such a protocol includes genetic counseling, disclosure of all relevant test information, informed consent, and avoidance of physician/investigator conflicts of interest in research study enrollment.

Psychological Consequences of Predictive Testing

Although some researchers argue that results from susceptibility testing can induce depression and suicidal ideation, others believe that testing may be beneficial. In a study of patients who were at risk for Huntington disease and underwent susceptibility testing, Wiggins and colleagues found that knowing the result of the predictive test, even if it indicated an increased risk of disease, reduced patient uncertainty and provided an opportunity for appropriate planning. They further noted that among those patients who tested positive for the altered huntingtin gene, none attempted suicide or required psychiatric hospitalization. These data suggest that the possible deleterious psychological effects associated with predictive testing are largely preventable. To minimize psychological trauma, physicians should assess psychological risk for all patients prior to testing.

Financial Constraints

As in the provision of many health care services, the decision to undergo genetic testing is partly financial. Who will pay for the test? Does the benefit outweigh the cost? Hessel Bouma III comments, “No society can afford to do all that medicine can do or all that it wants to do for all patients.” While it is inevitable that lack of financial resources will make it difficult for some patients to pursue genetic testing, stratification of patients by risk will increase the availability of appropriate tests for high-risk groups. A clear discussion of the cost, predictive value, and indications for the test can help the patient and physician reach an agreement on whether or not to pursue testing.

Insurance Discrimination Based on Test Results

Post et al argue that if Medicaid is substantially curtailed, private, long-term health care insurance may become the principal means by which persons with Alzheimer disease and their families gain access to medical care. As a result, private insurance companies may deny coverage to persons at risk for Alzheimer disease. Even when the results of genetic testing are not available, insurers may seek to identify applicants at increased risk for disease. Although the logistical problems associated with implementing anonymous genetic testing are formidable, it is imperative that genetic information be handled in a manner that maximizes confidentiality.

Technical Limitations

Because no genetic test can foretell disease with absolute certainty, genetic test results must be interpreted cautiously. In the case of Mr Smith, his family history indicates a genetic risk for early-onset familial Alzheimer disease (FAD). Early-onset FAD represents fewer than 15% of all cases of Alzheimer disease. Studies have shown that approximately 50% of the early-onset Alzheimer disease
patients have a mutation in the \textit{presenilin-1} gene on chromosome 14. The diagnostic accuracy of tests currently available for Alzheimer disease is reported to exceed 85\%. Still, discretion is required in interpreting test results, since neither a positive nor a negative screen for Alzheimer disease provides definitive information about the eventual emergence of disease.

“What should you do?” asks the physician, echoing Mr Smith’s question. She sighs as she places her clipboard on the table.

“You’ve been through a very long and painful ordeal with your mother. It must have been heart-wrenching to see her slip away without any solution from medical science. . . . The forgetfulness that you describe is most likely related to the stress that you have been under as you’ve been trying to juggle home life with three kids and a very ill mother.”

Mr Smith nods slowly as he fixes his gaze on his shoe tassels.

“Your mother died of early-onset Alzheimer’s disease, a disorder that is often inherited. It’s true that we have some accurate screening tests for some of the most common causes that cause early-onset Alzheimer’s, but I’m not sure if it’s the best idea for you to be screened, especially while you are mourning your mother’s passing. I want you to know that I will respect your decision be tested, should you decide to do so, but I’d like you to schedule some pre-test counseling with me first. I would be happy to give you a full physical and neurological exam to assess your signs and symptoms when you come in for the counseling.”

“Yes, that would put my mind at ease,” states Mr Smith, making eye contact with the physician again.

“The genetic test is not covered by your health insurance, and it will cost you about $600. The test is confidential and anonymous, similar to an HIV test, and the results will not go on your medical record. . . . I suggest that you think about this decision for a while, let things settle down a bit in your personal life, and call me if you have any questions about the test or your health. Do you feel comfortable with that?”

“Well,” Mr Smith sighs, “I think you’re probably right . . . this test needs to be given some thought, and my forgetfulness is understandable considering the circumstances, right?”

The doctor smiles at Mr Smith as she places her hand on his shoulder reassuringly. She then turns and walks toward the door.

“Doctor!” blarts Mr Smith. “You forgot your clipboard!”

“Ah, yes,” says the physician, smiling. “My memory is not what it used to be. Perhaps we are all in the same boat?”

References


\textbf{Indecision}

Warren Kinghorn, Harvard Medical School

[This is an excerpt; the full text is available on the MS/JAMA Web site.]

The decision about whether or not to be tested is ultimately yours, and yours alone, to make. You are a competent adult, and you have the right to make autonomous decisions about your body and your health care. You are entitled to know this information, just as you are entitled to know your blood type or your blood cholesterol levels. The information is within you, and it should not be kept from you.

Some might say, however, that beyond a right to know, you have a duty to know—that you ought to find out whether or not you will get the disease. You ought to be tested, they might say, so that if you do have the gene, your family can prepare for your illness, or you can avoid having a child that might also carry the gene. But this is surely misguided on both counts.

What does it mean, we might ask, to have a moral duty to do anything? This is an important and inscrutable question—the central question, in fact, of the branch of philosophy called ethics—and many people have answered it in different ways. But in your case, we may say that you have a moral duty to do what you believe will result in the greatest amount of good and the least amount of suffering for you and your family. If you have the gene, and you believe that you and your family would suffer less by knowing now rather than later, it is true that you have a moral duty to be tested. If, on the other hand, you feel that you and your family would suffer more if you know the results now—if you fear that the knowledge would harm your marriage, or estrange you from your siblings—then you have a moral duty not to be tested. It is certainly premature, then, for anyone to tell you, prima facie, that you have a moral duty to be tested for the \textit{huntingtin} gene.

In the same way, it is premature to say that you have a moral duty to keep from passing the gene on to your children. It is a serious thing to bring a child into the world who might suffer as your mother suffered. You may decide not to take that chance. But to consider it wrong, or to try to prohibit it, is unconscionable, vaguely reminiscent of the time when our government sterilized mentally handicapped people to keep them from procreating. Can we really presume that Huntington disease carriers would rather not have been born? Does the suffering in their lives outweigh the good which might derive from them? What if your mother, aware that she carried the gene and faced with a similar decision, had chosen not to give you birth? Would that have been a good thing or a bad thing? Is the potential suffering of a person too high a price to pay for his or her existence? These are tough questions, for you alone to decide; and only you can know if you ought to be tested.