Genetics in Medicine: Real Promises, Unreal Expectations

One Scientist's Advice to Policymakers in the United Kingdom and the United States

By Steve Jones

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Foreword

This report describes for policymakers the promise and limits of the application to health services of current research-based knowledge about genetics. The Milbank Memorial Fund commissioned this report from a noted scientist on behalf of an informal group of persons who make policy for purchasing health care in the United Kingdom and the United States. The members of this group are identified above. The Fund is an endowed foundation, based in New York City. It collaborates with policymakers in the public and private sectors to analyze, develop, implement, and communicate about health policy.

The group of purchasers met in London in 1997 and in New York the next year. The purpose of these meetings, as a British purchaser wrote, was to

> *consider the developments that have taken place…in relation to purchasing, as the process has become more sophisticated and specifically to address the issue of the information that purchasers need to purchase effective and cost-effective health care…Discussing the developments and limitations of the situation in [each] country in the presence of individuals from a different system, but with many areas of shared concern, is…likely to be mutually beneficial.*

The organizers of these meetings hypothesized that people who did similar work each day would find common interests despite the enormous differences in the organization and financing of health services in the United Kingdom and the United States. Moreover, focusing on common interests might reduce the tedious hours of elementary descriptions of national health care policies and systems that absorb considerable time at many international meetings.

The hypothesis proved correct. The UK purchasers—each of whom worked within the National Health Service—and the US purchasers—who served in the executive and legislative branches of government, private industry, and a public corporation—immediately found common ground. They described their systems and policies in the context of discussing problems in purchasing health services for populations.

The members of the group have completed three projects. This report describes the implications for policy of research on genetics. A report now in press assesses the extent to which purchasers in both countries use the results of research on the effectiveness of health care interventions. The third project convened experts in assessing health care technology from the two countries to explore practical possibilities for collaboration in the dissemination of information.

Many people deserve credit for this report. Alan Burns and Helen Darling led the group in formulating questions about genetics to which policymakers wanted answers. Ron Kerr recommended that we commission Steve Jones to write the report and helped to recruit him. John James and Barbara Stocking participated in describing the overall purpose of the group and recruiting its members from the United Kingdom. These people are identified by title above. Barbara Stocking, Regional Director, National Health Service Executive, Southeast Regional Office, could not participate in the ongoing work of the group. Professor Jones's achievements are described in more detail in a biographical note that follows the report.

Members of the group reviewed several drafts of this report. In addition, three scientists reviewed the accuracy and clarity of the scientific information in the report: Celia I. Kaye, Professor and Chairman, Department of Pediatrics, The University of Texas Health Science Center at San Antonio; Arthur C. Upton, President, The Ramazzini Institute, and Clinical Professor, Robert Wood Johnson Medical Center, Newark, N.J.; and Ron Zimmern, Public Health Genetics Unit, Strangeways Research Laboratory, Cambridge, U.K.

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Genetics in Medicine

The public is obsessed with DNA. Many doctors, too, are convinced that their profession will be transformed by modern biology. Geneticists, in contrast, are gaining a new realism regarding what their science may and may not achieve. The completion of the map of human DNA has focused their minds. Those who made it will have to justify the expense, and are already realizing that, despite undoubted advances, many early hopes were overstated. Although their science will do remarkable things, genetics may be used more for diagnosis than for cure. And, far from taking medicine into an era of Mendelian clarity, the study of human inheritance may remain full of ambiguity.

This essay puts genetics' profile into context and asks what effects it might have on medical practice in the next decade. In a field that moves so quickly, to make predictions is dangerous, but a look ahead suggests that the areas that will be most important are not those now most prominent. If this document appears too pessimistic, I plead reaction against the general tendency to accentuate the positive when it comes to human genetics.

Genes, Expectations, and Realities

Many expect too much from genetics because it seems to promise to answer questions that lie outside science altogether: issues of sex, identity, and fate that have occupied human beings since the Old Testament, the first genetics text of all. Genetics also overlaps with political controversies, abortion, cloning, and innate differences in behavior included.

Most people die of a genetic disease, but not many of them notice. However, the image of genetics was until recently that of a science of exceptions. Devastating though inherited illness might be, genetic disease was not high on most physicians' list of concerns. Genes were seen as responsible for severe inborn defects, but most were impossible to cure, so that those affected die young and relatively cheaply. Although some inherited diseases, such as cystic fibrosis, are treated with some success (and expense), each such defect is rare. With an overall incidence of around one in 100 live births, genetic problems were (or so it seemed) a significant but secondary part of medicine.

Now, genetics promises much more. Genes are, more and more, involved in common disease. That fact puts social issues into focus and, more and more, raises questions about where medical decision-making stops and society's values begin. The new genetics raises problems of confidentiality, of stigmatization, and of insurance, and demands a new examination of the whole balance of responsibility between individual, family, and community.

Some of its questions—those of the cost of treatment, the chances of success for new treatments, and adverse selection in an insurance-based system (with those who learn that they are at risk buying more coverage)—are familiar. Others are new. Inherited disease involves more than the individual patient. Genetics has the power to draw the whole population, healthy or not, into the medical net. It allows early diagnosis of conditions, some treatable and some not, that appear late in life. That may lead to the creation of a class with "presymptomatic disease," who turn to doctors for help that they cannot provide. In this new medical world the equations of cost and benefit begin to change. Careful decisions are needed when it comes to what information is gathered and to whom it is made available.

Hubris versus Realism

For twenty years geneticists have issued a stream of promises about what they will achieve. Few have been fulfilled, and some will never be. It has been said that the four letters of the genetic code are H, Y, P, and E, and medical providers must realize that the molecular biology business is as adept at promoting its wares as is any other.

There have been great advances since the discovery of the structure of DNA, and the map of the complete human sequence is, in effect, here. Medicine has already assimilated much of the new information. Improved techniques for prenatal diagnosis have led to a decrease in the numbers of children born with particular illnesses. Reproductive technology, too, helps to ensure that only healthy children are brought into the world.

Genetics has also helped in treatment. Some diseases can be treated with a missing-gene product—sometimes, as with hemophilia, with a protein made by genetically engineered animals. New tests permit early identification and treatment. All infants are screened for phenylketonuria, a condition that results from a genetic inability to break down an amino acid found in many foods. Those found to be at risk are put on a special diet that reduces the disease's severity. Other genetic tests help prevent damage. Those carrying the gene for familial polyposis coli are offered a treatment—excision of the colon—that is drastic but effective, if done early. Their relatives, too, can be screened and offered the same treatment.

Most such advances, as elsewhere in high-tech medicine, apply to only a few people. Their costs and benefits can be assessed in the same way as those of organ transplants. The main promise—and threat—of genetics comes from its potential to escape from the exceptional: to help diagnose and perhaps treat common ailments.

A century ago, our enemies came from outside: from microbes, violence, and starvation. Now that we are at less risk from infection, war, and hunger, we face the enemy within. More and more people are killed by our inborn weaknesses, which play a part in heart disease, diabetes, and cancer, among other illnesses. The germ theory of disease led to a new era of medicine. Perhaps the map of DNA will have an equal success by allowing disease to be predicted before symptoms appear, prevent it before damage is done, and cure it by molecular surgery.

Genetics will, perhaps, alter the medical landscape. However, a new realism is making itself felt within the field, and many geneticists now fear that such successes are farther away than they once appeared. Genes are certainly important in common illnesses, but patterns of inheritance are much less straightforward than they at first seemed. Because of this, genetics is likely to remain where it is today, within the ambit of preventive medicine. Enchanted with possibility, the public lacks a sense of what is feasible, and geneticists are (or ought to be) alarmed by the widespread tendency to hope for more than is justified and to enter into premature trials of therapies that seem almost doomed to failure.

What Is Genetic Disease?

To type "OMIM" into any search engine reaches the database Online Mendelian Inheritance in Man, maintained by the National Institutes of Health. A mass of data emerges. At the last count, 10,000 distinct genetic conditions were listed, by recessive (needing two flawed genes, one from each parent), dominant (a single gene doing the damage), and sex-linked loci (those carried on the X chromosome), with others due to many genes of small effect.

That number is large indeed. Most perinatal mortality has some genetic basis, and most long-term mental patients have conditions that can be ascribed to genes. All cancers, too, involve genetic changes, in body cells, in the germ line, or in both.

Although most of the illnesses listed are rare, the incidence of genetic damage as a whole is quite high. In populations of European descent, about one child in 2,500 is born with cystic fibrosis. Certain populations are at even higher risk: in parts of West Africa, one person in three carries a single copy of the sickle-cell allele, and by 2050 one child in 15, worldwide, will bear one or more copies of genes associated with abnormal red blood cells.

Mendel's rules show that there are far more copies of recessive alleles hidden within normal people than are ever exposed. One in 25 Europeans carries a single copy of the cystic fibrosis gene. This "genetic load" is reflected in the greater incidence of ill health among the offspring of relatives. Marriages between cousins suggest that every person bears, on average, a single copy of a gene that if present in double copy would be lethal. Damaged genes are not exceptional, but normal.

What Is Not Genetic Disease?

Ill health runs in families. Usually, this has rather little to do with genes. The best predictor is simple: class. Tuberculosis and lung cancer (like rickets in the 19th century) may soon be diseases of the poor, and even for conditions such as cancer, the chances of survival are related to income. Wealth and poverty are inherited, and most people born poor stay that way. In Britain, the difference in life span between the most and the least affluent is 11 years, which dwarfs anything that DNA might do. As familiar as all this is, and as important to public health as it might be, nobody sees this as falling within the province of genetics.

In the 1930s, pellagra—a deficiency of vitamin B—was identified as a "Mendelian" illness because it was passed from parents to children. When its real cause was discovered, the genetic hypothesis was abandoned. Today's nutritional problems are involved more with excess than with lack, but such illnesses still run in families. Obesity, coronary artery disease, and diabetes are concentrated among those with poor diets—the poor themselves. Heritable though such conditions are, to change eating habits would do more to improve health than could the most optimistic molecular biologist.

The boundaries between "external" and "internal" causes of illness are far from simple. Susceptibility rather than certainty is coded into the DNA. Vitamin supplements given to women who have had one child with a neural tube defect reduce their risk of having another, although genes are involved in the condition. If everyone smoked, lung cancer would be a genetic disease.

The interaction between nature and nurture makes it hard, as a result, to exclude *any* illness from the territory of genetics. More and more inherited weaknesses are emerging, and more and more genes that respond to environmental stress are being tracked down. The new genetics reminds us of what medicine has always known: that nurture and nature work together. Genetics allows us to understand that interaction with greater precision and to identify those most at risk.

The Allure of Technology

To complete the map of DNA was a triumph of genetics as a science. Its success as a technology, however, has yet to be established. It can be hard to translate theory into practice. Vesalius worked out the anatomy of the heart in 1543. Eighty years later, William Harvey sorted out blood circulation, but the first heart transplant was not performed until 1967.

The double helix was discovered less than half a century ago. Since then, genetics has been transformed. Its techniques range from novel staining methods for chromosomes to the polymerase chain reaction that has revolutionized gene sequencing. The Southern blot matches a DNA sequence with others suitably labeled. In this way, a gene can quickly be tracked down. That idea has been developed into the "DNA chip," in which tens of thousands of targets are put onto a plate and used to search for mutations.

Such technology means that medicine is now able to work from the bottom up (from gene to receptor protein to potential drug, for example) rather than, as in earlier times, starting with a disease and trying to infer its basis. Genetics is the first science to accelerate by going into reverse. To find out what genes do no longer depends on the existence of an inherited abnormality. As a result, much of medical research has become genetic research, and large parts of medicine have, somewhat to physicians' surprise, become genetics.

Without difference, there could be no genetics, and a start has been made on mapping variation among people and populations. About one DNA base in 1,000 varies from person to person, and a world map of variable sites is now being drawn. To understand the relation between the inheritance of DNA variations and patterns of disease is a crucial step toward identifying wayward genes.

There is now a free market of genes, with the potential of moving DNA from any organism to any other. Genetic engineering is used by agribusiness and pharmaceutical companies. Some proclaim that the 21st century as the "post-genomic era": the time when the language of the genes will be translated, and we will understand what every gene does and how it interacts with others on the journey from egg to adult. But it is worth remembering how little impact most of this science has had on the practice of medicine. Although the treatment of inherited diseases has improved, genetics has not played much of a part. The error behind sickle-cell anemia has been known for 50 years, but what treatments are available have emerged from empirical medicine. The same is true for cystic fibrosis. The genes for Huntington's disease and muscular dystrophy were among the first to be identified, but these discoveries, too, have not led to treatments. In the same way, many inherited cancers are no more curable than they were before their genes were discovered.

The value of discoveries in genetics to medical practice has yet to be established.

The Search for Cures: Therapy, Clones, and Xenotransplants

The idea of repairing damaged DNA has been around for a long time. The first claims were made in the 1980s, but the idea remains more a hope than a reality. Supposed successes with, for example, the replacement of the enzyme lacked by children with severe combined immunodeficiency (the "boy in a bubble" syndrome) are complicated by the fact that (with one exception reported in early 2000) children treated with this therapy are receiving other treatments as well. Likewise, the many attempts to reduce the severity of cystic fibrosis with DNA-based medicaments have had equivocal results complicated by unwelcome side effects.

Other claims of success in the treatment of various cancers and other inherited diseases are too premature to be assessed. Adding to the confusion is the use of the term *gene therapy* in a sense much wider than its original, to include, for example, the treatment of heart disease with proteins that stimulate the formation of capillaries. Those involved in such research still disagree about which delivery method is best, as well as about a host of other practical and theoretical issues. At least for the time being, this technology seems unlikely to play a large part in medicine. The situation might change, and there are real prospects in some areas—for example, drugs designed to target cancer cells. But, for now, gene therapy (however defined) has a marginal role in the clinic no matter how exciting its prospects in the laboratory.

Neither is cloning, in its usual sense, likely to have much practical impact. Claims that human cloning is imminent are hard to take seriously. Even without legal prohibitions, its many difficulties (a low success rate, with a high incidence of birth defects in cloned animals) means that this technology will not soon affect human reproduction or medicine. Less ambitious forms of cloning, however—such as cloning cells to replace missing white blood cells or to make sheets of skin cells that match a donor—are much more feasible.

Stem cells (very early embryonic cells together with cells from a few adult tissues) differentiate into particular tissues, and might even be persuaded to make whole organs or parts thereof. Because such cells may be obtained from surplus embryos created through artificial fertilization, objections have been raised to the research, but it has much promise. And xenotransplantation, in which immunological cues are altered to prevent, for example, the rejection of a pig's heart transplanted into a human body, is also under investigation. The potential risk of transfer of viruses between species seems less important than it did. If the method succeeds, a new weapon will be added to the surgeon's armory and geneticists will be drawn into a new field of medicine.

In other areas, too, genetics is involved in the practice of medicine. Already, in vitro fertilization has a success rate per attempt higher than does conventional sex. Egg and sperm donation are widespread (as is surrogate motherhood), and early embryos can be checked for liability to genetic disease before implantation.

The Ubiquity of Error

Everyone, in the end, dies, and genes are often involved in that unpleasant process. Nobody escapes from the fate coded in DNA: aging takes place as mutations build up in cell lineages, and cancer is a genetic disease of body cells.

Ancestry changes the risk of illness. Cystic fibrosis, common among Europeans, is not found in Africans. Finns have many genetic diseases unknown elsewhere. Mediterraneans are of particular risk of thalassemias, while some Jewish groups have a high incidence of Tay-Sachs disease.

To suffer from a genetic disease at some time of life or to be a carrier of a gene that in double copy causes severe illness is not rare, but universal. That is the greatest challenge of genetics. To map the genes should, perhaps, make it easy to test those at risk of inherited illness, and many feel that a new era of certainty has dawned. The truth is, alas, less simple.

Life Goes Wrong in Many Ways

There are two problems in applying Mendel to mankind. First, for most Mendelian illnesses, any gene can be damaged in a number of different places. Every population—sometimes, every family—may have its own

mutation within a structure that may be tens of thousands of bases long. As a result, a test that detects an inherited error in one group or family may not work for others. To speak of "the" test for, say, cystic fibrosis means less than it seems.

In addition, the accidents of history mean that there is a great variety of damaged genes. Some mutations happened long ago and have spread to millions. Others have taken place recently and are found in only a few. In hemophilia, for example, almost every affected family has its own variant. Some genes (such as those responsible for some breast cancers) carry a mixture of ancient and modern mutations.

In general, the older a mutation is, the more widely it has spread and the easier it is to generate a useful test. But for the hundred or so most frequent Mendelian diseases the news is not particularly good: most have high mutational diversity, most individual mutations are rare, and the majority, most probably, have appeared within the past 2,000 or so years.

All this means that to establish carrier status is not easy. Cystic fibrosis may arise from more than 1,000 different errors, some common and some rare. One is responsible for 70 percent of the cases in western Europe, but, 2,000 miles to the east, that mutation causes only a small fraction of cases. In Jewish populations in the United States it is involved in only about a third of cases, but among North African Jews quite a different mutation is most common. A single illness, the result of errors in a single gene, has a multiplicity of causes.

The accuracy of tests will no doubt increase. Multiple mutations mean, nevertheless, that screening will remain ambiguous and that a negative result does not mean safety. A general screening for all common genetic diseases is, for the time being, not feasible.

DNA Is Simple, But Illness Is Complicated

Many ailments that at one time appeared to be single diseases have been subdivided. "Fever" was one single disorder with a single treatment, and much the same was true of "cancer." Such views began to change long before genetics, but advances in genetic science have speeded up the process.

Nobody doubts that cystic fibrosis is a single illness. However, most inherited diseases are not due to errors in a single (or even a few) genes: instead, they are symptoms of a great constellation of failures. Sometimes a single error is involved in certain cases but not others; sometimes, inherited changes whose individual effects are imperceptible may together produce a disease. The genes at fault may differ from place to place or from family to family. Often, a genetic problem may not show itself until it is exposed to a particular challenge. Because some conditions (heart disease and many more) have a largely environmental origin in some patients and a mainly genetic one in others, to unravel the causes will not be easy. Even then, it is not clear how useful the information will be.

Diabetes mellitus is a state of glucose intolerance. The cause, a loss of control of blood sugar, seems simple. It leads to kidney damage, nerve destruction, and death and, in the United States, costs $100 billion a year to treat. The disease comes in two flavors. One, the insulin-dependent form, results from a failure of the secretory glands of the pancreas. Juvenile diabetes, as it is often called, affects about one child in 1,000, appears early, and can be treated with insulin. The other variety, non–insulin-dependent diabetes mellitus (NIDDM), is milder, appears later, and is resistant to that treatment. At least 6 million Americans have the illness without knowing it, and it is becoming more common. The diseases, similar though they seem, present medicine with quite different problems.

Genetics shows not only that "diabetes mellitus" is actually two or more distinct diseases but that some are influenced by inheritance and some not.

It was once thought that insulin-dependent diabetes was caused by viruses, or by diet, or even by living in towns. None of those ideas was sustained. Genes are involved, in particular those of the immune system. Siblings of diabetics have a risk of the disease 20 times higher than does the general population. Even those without relatives known to have the disease, but with certain combinations of cell-surface antigens, face a tenfold increase in risk. Early-onset diabetes, is, it appears, an autoimmune disease.

Variation in one gene explains a third of the family clustering. At least 20 others—some involved in the insulin machinery and others at work in unrelated parts of the cell—confer a predisposition to the disease. As identical twins have only a one-in-three chance of both being affected, an unknown environmental agent is also involved. This form of diabetes is, it seems, a disease in which the underlying variable, insulin

production, and the threshold at which illness sets in, vary from person to person.

Because the genetic component may sometimes be strong, a DNA test can be used to identify some children at risk and to begin treatment before any damage is done. But, most patients—those with genes of minor effect, or those exposed to the unknown environmental stress—will not be helped by a genetic test.

NIDDM is even more complicated. Genes play a part, but they separate populations rather than individuals and manifest their effects only in certain conditions. The disease is common among those of Pacific Islander, Native American, or Asian ancestry. Although the illness runs strongly in families, no single gene accounts for more than a tenth of individual susceptibility. Many genes, scattered through the genome, are involved, but we have little clue regarding how they lead to illness. A search in the United States for the 11 genes thought to be involved in NIDDM in the British population turned up only two.

The most striking aspect of NIDDM is the power of the environment. The illness is rare in Native Americans living in rural Mexico but common among their descendants in the United States. A difference in diet is to blame. Native Americans are genetically less able to cope with carbohydrates than are Europeans, but those living in the United States consume much more of that material than do their relatives in Mexico, and the illness follows. In this group, one gene has a relatively large effect and might be used as a test for those most at risk, but for non–insulin-dependent diabetes genetics as a whole is a much less effective predictor than is diet. A change in lifestyle would benefit the whole population, whatever their genetic predisposition.

Is diabetes—once thought of as a single disease—two, or more, or many, each of which may require a different treatment? Certain patients may be detected before symptoms appear, but others will be missed by any screening program. Drug therapies help some but not others. A few people will develop diabetes whatever their diet, while others may, despite an inherited susceptibility, avoid the illness because of the way they live. In the end, it seems, genetics has little relevance to the treatment of NIDDM; banning cheeseburgers would do far more.

Many, perhaps most, diseases are rather like this. Breast cancer kills thousands of American women. Two genes, BRCA1 and BRCA2, are implicated in about one case in 20, but the majority of cases cannot be attributed to specific genes at all. What is more, one in five of all carriers of the BRCA variants do not develop the illness. The case is similar for Alzheimer's disease: most sufferers have no overt genetic predisposition, although homozygosity for the Apo E4 allele may bring the probable date of first symptoms forward by almost 20 years.

Cardiovascular disease is likewise complicated, with both genes and environment involved. Some families inherit a tendency toward high levels of blood cholesterol, but almost 200 different genotypes can generate the effect. As a result, such families can be more readily identified with a simple blood-cholesterol test than with DNA analysis. The best predictors—smoking, obesity, and a family history of heart disease—need no technology at all.

The problems of multiple loci, multiple alleles, and unknown environmental factors mean that research on the genetics of common illnesses has been plagued with findings that cannot be replicated. The many claims that genes are associated with mental illnesses such as schizophrenia and depression have for the most part not been sustained. Icelandic researchers' claim to have discovered genes predisposing to multiple sclerosis was soon retracted. Despite plans for huge (and expensive) sweeps through the DNA undergrowth the chances of success in tracking down genes for such conditions are not high.

When Screening Is Useful

Screening to predict future health is not new. All doctors routinely check their patients for high blood pressure or for glaucoma, and healthy women are regularly screened for early signs of breast cancer. As technology advances, early signs of other common cancers (such as prostate cancer, which can be signaled by the appearance of specific antigens long before signs of abnormality) can be checked. DNA research brings the prospect of better diagnosis, with tests for a variety of diseases, both inherited illnesses and those that arise through mutations in body cells.

Some of DNA testing's potential goes unrealized. A million Americans are at risk for hemochromatosis, which leads to a failure of iron metabolism and damage to the heart and liver. Untreated, it can be fatal. Among whites, about one person in 400 inherits the disease, and it is even commoner among those of African ancestry. The gene has been cloned, and most hemochromatosis patients carry one of two mutations. Treatment is cheap and simple, involving the occasional opening of a vessel to let enough blood

to prevent the buildup of iron. Effective screening could save 1,000 lives a year and avoid a great deal of expense. No such screen is planned.

Genetic tests are also likely to be useful in assessing the effectiveness of drug treatments. "Pharmacogenomics" began with the discovery that suxamethonium, a muscle relaxant used in surgery, was lethal to those few patients who had a rare version of a gene involved in nerve transmission. Now all are tested before the drug is used. To tailor medicines to patients may become common. Individuals show very wide variation in their ability to deal with anti-cancer drugs, and, as a result, a dose helpful to one genotype may be fatal to another. Conversely, certain drugs not now widely used because of their toxicity may be safe for some people. In the future, different treatments may be prescribed for different forms of the "same" illness (e.g., asthma, schizophrenia) when genetic tests reveal that these are distinct conditions.

A propensity to suffer side effects may also have a genetic basis. One woman in 25 carries the "Leiden" form of a certain gene in the blood-clotting pathway. Such women who use birth-control pills face a 50-fold increase in the risk of heart attack. It might be a medical system's duty to screen its young female population for this allele. However—as with many screening programs—to do so might have undesirable consequences, causing undue concern or convincing some women to give up the pill, thus exposing them to an increased risk of unwanted pregnancy.

Genetic screening inevitably raises the issue of abortion. Many geneticists are concerned by the readiness of potential parents to terminate on insufficient grounds: thus, some clinics will not reveal to parents that a fetus carries the gene for achondroplastic dwarfism, a mild disorder, while others do. The abortion issue is often skirted around by geneticists anxious to avoid controversy, but will remain central to the science for the foreseeable future.

Some Orthodox Jews, opposed to abortion, have come up with a way of dealing with it that circumvents the possibility that pregnancy termination will ever be an issue. Children are tested at school for the presence of Tay-Sachs and other errors, and their carrier status anonymously recorded. When a marriage is planned the records are checked, and in the few cases where both partners are carriers the marriage broker is informed and the process halted. This ingenious idea means that carriers need never know their status unless they are considering a marriage to another carrier. The program is a great success, but it is unlikely to become widespread.

If particular conditions could be cured before birth, prenatal screening would probably be universal. At present, most screening is performed with the possibility of pregnancy termination in mind and hence is unacceptable to part of the population. What people actually do when faced with the reality of bringing an unhealthy child into the world is hard to predict: in Catholic Sardinia, where the inherited blood disorder beta-thalassemia is widespread and where the Church is strongly opposed to abortion, the number of children born with the condition has dropped dramatically since prenatal diagnosis was first offered. Nobody denies that selective termination is not an ideal outcome for genetics to aim at, but for the immediate future it will be the main purpose of prenatal screening. If a couple, or a society, is not willing to accept this, then screening has little value and offering automatic screening for all inherited illnesses makes little sense.

Other Limits to Screening

Screening can be too powerful for its own good. If nothing can be done for a condition, what is the point in diagnosing it? Many—perhaps most, given the role of genes in aging—diseases of late onset fall into this category. For some illnesses, those at risk are already aware of this problem. Half of those with a parent with Huntington's disease are at risk; because the first symptoms may not appear until middle age, they live for many years in a state of uncertainty. In Britain only about a tenth choose to take the test; doubt, it seems, is preferable to certainty. In contrast, half of those at risk of breast cancer (for which early drug intervention might help) agree to be tested, and 80 percent of those at risk for familial colon cancer, which can be helped by surgery, accept screening. Whether a condition is treatable is central to the value of genetics.

Although a national demand for tests for carrier status should be resisted on grounds of high cost and low efficacy, it may be hard to avoid large-scale screening because of the increasing availability of over-the-counter tests. Kits for home testing for pregnancy and blood-cholesterol levels are being joined by self-administered checks for inherited illnesses. Already, such tests are commercially available for cystic fibrosis carrier status and for genes predisposing to breast cancer, and with the development of DNA "chips" many more will soon be on sale. They are marketed as services rather than as products. As a result, the Food and Drug Administration, strict though it is in assessing new drugs, sees them as outside its jurisdiction. The

interval between the discovery of a gene and the marketing of a test for may be short, and doctors will have to deal more and more often with those who have diagnosed themselves, rightly or wrongly, as being at risk of inherited disease. To assume that the free availability of tests will lessen the pressure on a health care provider is as unreasonable as to claim that pregnancy tests do the same thing.

Screening also raises problems of discrimination against carriers, particularly when it comes to insurance. Employment opportunities may also be at risk. Nobody wants to travel in an airplane with a color-blind pilot, and those with the gene are denied entry to the profession. This logic could extend a long way. For example, people who inherit certain forms of the alpha-1 antitrypsin enzyme find it hard to deal with dust and atmospheric pollution, and some individuals with particular forms of the proteins used by the body to detoxify poisons might be unduly susceptible to industrial carcinogens. As more genes whose effects impair the ability to perform certain kinds of work are identified, and as tests for these genes become available, we may see widespread demand for genetic screening as part of the hiring process.

Genetic discrimination might, by excluding those most at risk, be used as an excuse by industry to avoid the need to maintain safe exposure levels. The legal situation is patchy. During the 1970s, several states passed laws prohibiting discrimination against carriers of the sickle cell gene, and these have been extended. Wisconsin allows genetic testing in employment, but only if the employee requests it, while in 1996 New Jersey passed a law forbidding the use of such information altogether. New York, by contrast, allows the employer to use tests if there are occupational risks, even without consent. The federal Americans with Disabilities Act of 1990 gives some protection against discrimination on the basis of genetic disease, but it is not clear how much. The Health Insurance Portability and Accountability Act prevents insurers from using such information to deny coverage to those who change jobs.

Screening is, however, a two-edged sword. A company that uses genetic screening in hiring could just as well argue that it does so out of concern for employees' health and safety. And the new genetics may help inform individuals about their own risks and allow them to make decisions about reproduction, employment, or lifestyle on the basis of that knowledge.

After Screening: The Need for Counseling

Geneticists now recognize the importance of careful counseling after a positive test—a process that may involve ongoing contact over a long period. Of course, the disclosure of inherited disease need not result from a test. Many new cases of genetic disease occur in families with no history of the illness and carrier status is diagnosed when an affected child is born. It is then often easy to work out the chances of each successive child being affected. After the event, some couples choose to have no more children to avoid the risk of another abnormal birth. Some undertake another pregnancy, previously unplanned, to compensate for their earlier experience. No matter what the decision, the physician's role as an adviser increases. And, of course, those found positive on a commercial test may likewise turn to their doctor for advice.

The test itself may be cheap, but long-term follow-up is expensive. Should a carrier family decide to continue with reproduction, there will be the costs of prenatal diagnosis, counseling, and, possibly, termination. As many as four trained coworkers—specialist nurses, for example—may be needed for each clinical geneticist. They explain the nature and predictive value of the test and assess patient response. The response may depend on how the information is presented. Thus, in one British survey, 10 percent of women responded to a letter offering a cystic fibrosis carrier status test by mail, a quarter to a test made during a medical appointment, and almost three times as many when offered an immediate test, face to face.

Counseling for diseases of middle or old age (most of which are not curable) may help people to make decisions about their own lives, but it is not clear that providing such information is the responsibility of medicine.

Educating the Public

There is an urgent need for public education in genetics. That might seem an odd statement in view of its extensive coverage in the media. No doubt, the information storm will continue, and much of what is published is of high quality, but, more than anything, the public needs fair assessments of what genetics can and cannot do.

Education has already proved its worth. The alpha-1 antrypsin "Z" allele increases the risk of emphysema

among smokers. Among whites, the frequency of homozygotes is around one in 5,000, and half of all smokers with that genotype die before reaching age 40, compared to an average life span of more than 60 for homozygotes who do not smoke. The discovery of risk can change behavior: for example, in Sweden one in ten teenagers told that they have the ZZ genotype smokes, compared to one-fifth of those in the control group. The importance of disseminating such information can also be seen in Mediterranean countries with high levels of genetic disease, such as thalassemia. As the public has been informed of the facts, the amount of time and money spent on individual genetic counseling has decreased even as the number of terminations has increased.

More and more turn to the Internet for help. Although there are a number of good technical sites for professionals, and even more aimed at the general public, the information on genetics available online is diffuse and sometimes inaccurate. There is a real need for some objective body to set up a Web site for laypeople that would convey legitimate and up-to-date information in a nontechnical way—a nonspecialists' version of the NIH's Online Mendelian Inheritance in Man site.

Although reality is harder to sell than hopes and fears, there should also be a concerted attempt to encourage the media to run stories on the actual prospects of genetics in medicine. The constant repetition of breakthroughs with the discovery of the gene "for" this or that condition helps create and sustain unreasonable expectations. Clinical educators, too, might be reminded of the limitations of genetics, and avoid their students wasting money on genetic tests and technologies that may be useless.

What Is Genetics For?

Health policymakers must always ask what a technology offers, what it costs, and how its worth is measured. For most of medicine—whether heart transplants or Nuclear Magnetic Resonance machines—the figures are fairly easy to gather. For genetics, however, both costs and benefits may be more ambiguous.

Under what circumstances should screening be offered? An overall strategy is needed, not a series of ad hoc responses. Among the variables that must be considered are the age of a mother (given the well-known relation between chromosomal error and maternal age), the relatedness of the parents, whether they already have any genetically impaired children, the history of genetic disease in their families, their attitudes toward abortion, and the availability of treatment. There is inconsistency in the provision of screening even in the centralized British health system, and the potential for confusion is even higher in the United States.

Many individual single-gene diseases are so rare that it is economically infeasible to test for or to treat them within a small area. Although advocacy groups may exert pressure, the fact that many conditions have an incidence of only one in 10,000 or so may make it necessary for even the largest health management organizations to form consortia. Perhaps each organization might specialize in one or a few rare diseases, and exchange patients with others.

Because genetic diseases affect entire families, not just individuals, it often happens that people found to be at risk by one provider of health care lead to others who are the responsibility of another. This, too, calls for high-level cooperation. "Proxy diagnosis"—the inadvertent discovery that a third party, a relative of the patient, is at high risk of disease—raises legal questions. Is it a physician's duty to ignore the rules of confidentiality and inform other family members, even those outside his own care, of their situation? Or should the responsibility to inform relatives belong to the patient? (These are not academic questions. Physicians have been sued for not telling relatives of a death from inherited colon cancer because the information might have allowed those at risk to protect themselves.) And how long must a hospital keep in contact? As more accurate tests emerge, as they will, these questions will become more urgent.

As the genetic web spreads, and as geneticists' responsibilities to the general population grow, more experts will be needed. Clinical geneticists are rare (in Britain, only a couple of hundred to serve 60 million people), but, as science advances, every doctor will face genetic problems in his or her practice. At present, physicians themselves often explain risks to patients, identify affected family members, and help in counseling. Perhaps these tasks will become the job of specialist nurses, with a system of certification and a clear career path. Some American schools are already offering master's degrees in genetic counseling, but this kind of training is not so readily available in Britain.

Laboratories carrying out genetic tests face familiar issues of quality control. There have been a few widely publicized errors in forensic work and paternity testing, and, although some degree of error is unavoidable,

mistakes in genetic testing are particularly dangerous, since a false result is liable to draw in not one but many people, with increased risks of litigation.

How is a successful genetics program to be defined? Much of the science involves dealing with healthy people, either carriers of single copies of recessive alleles or those suspected of bearing alleles that might affect future health. Other aspects involve the testing of those at risk of having children with genetic disease. The possibility of pregnancy termination is ineluctably part of this process, but assessing success by the number of pregnancies ended is not a satisfactory way of presenting a program's merits to the public, even though abortion reduces the incidence of disease at least as well as anti-smoking propaganda reduces lung cancer. And what of a woman found to be carrying an affected fetus who decides to continue with the pregnancy—is this to be counted as a success or a failure?

Screening is often cost effective, at least in the starkest sense. In the Netherlands, the national genetic counseling service costs about $50 million a year. It prevents the birth of 800 to 1,600 of severely handicapped children annually. Even in that country's cost-effective health care system, the expense of lifetime care for those children would be between $500 million and $1 billion. For the United States, with a population 20 times larger (and with certain segments at higher risk because of sickle-cell disease) the figures must be multiplied many times over. To take just one example, for fragile X syndrome (a common cause of inborn mental defect) the cost of preventing of a single birth is $12,000 as against the million-dollar cost of lifetime support.

Accurate though such figures might be, they are not palatable to the public. Given that disaster, more acceptable measures of success—for example, a high proportion of families at risk of hereditary cancer being enrolled in a screening program—are called for. Escaping its negative public image is one of the biggest difficulties faced by genetics.

Envoi

In some ways, the new genetics is no more than another form of high-tech medicine, of crucial importance to a few but irrelevant to the many. At present it suffers from too much publicity and too few results. Geneticists are in part to blame for overstatements and false hopes. But others are also at fault—those, for example, with ethical or political objections to the science, who also stand to gain from exaggerating what genetics might do.

Because inherited disease is, by definition, shared among many individuals, advances in genetics have the potential to draw more and more people under the aegis of medicine and to create a medical environment in which consultations with healthy people become more and more common. An insurance policy is a gamble that depends for its success on one party having better information on the risk involved than does the other. Genetics changes the balance: as more people become aware of the probable dangers coded within their cells, they may alter their expectations, their behavior, and their demands on their insurers. The problems of ethics and privacy raised by genetics go beyond those found in much of the rest of medicine. To deal with such problems while increasing our understanding of the complexities of inherited disease is the challenge faced by the new genetics.

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