CHAPTER 16

Testing Adults for Genetic Disease

Diabetes, Breast Cancer, and Huntington's Disease

This chapter discusses ethical issues in testing for genetic diseases using cases of three adults whose symptoms may not appear for many years. Perhaps the most important case involves Maria, a 30-year-old mother struggling with type 2 diabetes who represents 25 million people in North America with diabetes and 50 million who are prediabetic. The most famous case is that of Nancy Wexler, whose mother died of Huntington's disease and who has a 50 percent chance of inheriting her mother's disease. Finally, we discuss Joan, a 50-year-old mother and survivor of breast cancer, who, like Maria, has several daughters. Ethical issues in these cases of testing arise about families, personal responsibility, and money.

CASE 1: TESTING FOR DIABETES

Maria Lopez, a 30-year-old woman, has type 2 diabetes and struggles to control it.[1] Her extended family in East Harlem in New York City includes many older diabetic relatives. At 5 feet, 6 inches, Maria weighs 267 pounds and considers herself overweight. She has always fought to control her weight, finding it hard to exercise, and loves French fries and soft drinks. Diagnosed with diabetes at age 15 after she was hospitalized for spells of fainting, she once lost 100 pounds, but has since gained it back.

Diabetes mellitus is a disease of high blood sugar levels (hyperglycemia) caused by insufficient secretion or function of insulin, a hormone produced by the pancreas. *Type 1 diabetes*, once called juvenile onset diabetes or insulin-dependent diabetes mellitus, has low or no secretion of insulin. *Type 2 diabetes*, once called adult-onset diabetes, obesity-related diabetes, or noninsulin dependent diabetes mellitus, has resistance by the body's cells to insulin.

Diabetes may soon reach epidemic proportions: The Centers for Disease Control estimates that 21 million Americans suffer from diabetes and another 41 million are prediabetic.[2] At some point during their lives, one of three American children will become diabetic. Worldwide, more and more people who previously

avoided diabetes will succumb to it as they adopt Western diets high in fats and processed corn sugars. Americans of Chinese, Korean, and Japanese ancestry develop type 2 diabetes at a rate 60 percent higher than whites.[3]

Worldwide, 171 million people suffer from diabetes. That number is expected to double by 2030.[4]

In 2006, epidemiologists discovered an epidemic of type 2 diabetes in New York City. Over 800,000 of its citizens, more than one in eight, have diabetes.[5] This incidence in this city is a third higher than in the nation. In East Harlem, as many as one in five people has diabetes.[6]

Maria Lopez says her diabetes makes her miserable. "I have never wanted this disease to control my life." Since she was first diagnosed, she has denied that she has a disease and that it could lead to her early death. "I'm a traditionally-built woman from a culture of strong, big women," she says. "I eat what I like. To hell with needles and machines."

Diabetics must monitor their blood sugar several times a day. In the past, they had to do so by drawing blood with needles, but new technology now avoids that. Nevertheless, Maria and others find it socially embarrassing to constantly take out monitors to check their blood sugars, so they frequently omit doing so and fake numbers on their daily sheets.

Diabetics are told to give up beer, cokes, French fries, potato chips, pies, cakes, and "everything else that tastes good," Maria says. But many diabetics in East Harlem are poor with high levels of stress, are trying to keep families and jobs together, live around people whose lives have been affected by drugs, violence, divorce and unemployment, and hence find it difficult to eat right.

Public health educators urge Maria to exercise daily and to eat a low-fat diet high in fresh fruits and vegetables. "That's not so easy to do," she says. "And my two daughters (aged 10 and 8) like to go to McDonald's." Blood sugar monitoring is time-consuming and requires effort, and many patients dislike it.

Uncontrolled diabetes leads to very bad results: kidney failure, retinal damage that leads to blindness, gangrene (especially in legs, leading to amputation), damage to nerves, and heart failure.

In public health and primary care, diabetes is a stealth epidemic. "It's the Rodney Dangerfield of diseases," says the director of a diabetes center.[7] Compared with cancer and AIDS, less money is allocated to find cures for diabetics. Most medical care is oriented to managing crises rather than preventing diabetes.

In 2006, scientists at DeCode Genetics discovered a gene for type 2 diabetes. People who get two copies of the gene from their parents have twice the likelihood of developing diabetes as those who don't carry any copies. Being born with one copy raises the risk above average by 40 percent, and about 38 percent of Northern Europeans carry one copy of the gene, as well as many African-Americans. The head of DeCode explained:

> "If you have one copy of this variant, which 38 percent of people do, your risk of developing type 2 diabetes is increased by 40 percent," Stefansson, who is chief executive officer of DeCode, says. "Seven percent have two copies and have a 140 percent increase in risk."[8]

He also noted that he saw variants of this gene in other populations around the world not present in Iceland, where DeCode has a license to test the country's population for genetic diseases. Presumably, Far Eastern Asians carry a similar gene, explaining the incidence of diabetes in this population when they migrate to developed countries.

One philosophical question we want to consider in this chapter is this: Is Maria *responsible* for her diabetes? Normally, we recoil at this question because we realize that if we hold her responsible, she can be blamed for her disease. It's bad enough to have diabetes, why add to that by being moralistic?

Moreover, using the Golden Rule, we imagine what it would be like to get a diagnosis of diabetes ourselves: Do we want a moralistic physician or nurse condemning us, saying, "You should have eaten better! Now you have nobody to blame but yourself."

And if type 2 diabetes is genetic, then isn't such blame incorrect? Wouldn't Maria have gotten diabetes anyway, no matter how she ate? In the words of the debate over free will, isn't it false that she "could have done otherwise"? Even if her disease is partly environmental and due to poor diet, didn't something cause her to *crave* bad foods? Prediabetic people crave sweets, but some people with different genes have no sweet tooth and do not. So isn't blame about diabetes just stupid? Later in this chapter, we return to this question and provide some answers.

BACKGROUND: BASIC GENETICS

The gene is the basic unit of heredity. It consists of DNA, an organic molecule. Packed inside each of the 46 chromosomes in humans is a complicated strand of interwoven DNA, the famous double helix. The number of genes varies on each chromosome.

The pattern of the four nucleotide bases (A, C, T, and G) in the 46 double helices makes up a person's genetic code. Between 30,000 and 40,000 sequences of these 138 billion pairs of bases are genes.

The Human Genome Project, one of the greatest projects in the history of science, began in October 1993 with the goal of mapping which parts of human DNA were genes. Costing $3 billion, it finished in 2003, having mapped all the human genes.

Francis Collins headed this project. According to a biography about him, he

> developed innovative methods of crossing large stretches of DNA to identify disease genes. . . . That gene-hunting approach, which he named 'positional cloning,' has developed into a powerful component of modern molecular genetics. In contrast to previous methods for finding genes, positional cloning enabled scientists to identify disease genes without knowing in advance what the functional abnormality underlying the disease might be.[9]

Collins's lab also identified the first known gene for cystic fibrosis.

If we think of the 46 strands of human DNA (each with billions of base pairs) as, say, North America, the Human Genome Project showed the territory and its major highways; on this map, the 30,000 to 40,000 genes are the towns and cities. The largest gene, comparable in size to Los Angeles, is the gene for muscular dystrophy, composed of 2 million base pairs. The genes for globulin and insulin are like towns, with only about 1,000 base pairs each.

Knowing which parts of DNA are genes, and where they are, begins genetic knowledge. In the next steps, scientists must identify what genes do, with what other genes, and through which mediating proteins (proteinomics). In addition, some genetic diseases stem from variants in standard genes, or from nonfunctioning genes, so the causes of disease are complex. Finally, varying environmental inputs determine how many genes express themselves. Exposure of the fetus to drugs, nutrition in childhood, and use of tobacco affects how genes control bodily characteristics. In genetics, this is called the *norm of reaction.*[10]

Genetic diseases are inherited disorders. Some genetic diseases are caused by a dominant gene, as in Huntington's disease, where just one copy of the bad gene is needed to get the disease. However, most of us carry genes for recessive genetic diseases, but are not affected by them. We are *heterozygous*, having a dissimilar pair of genes for an inherited recessive disease. Heterozygotes of recessive traits will not experience a disease, but can pass the gene for it to their offspring. If two parents who are heterozygous for a disease both bequeath the gene for the disorder to an offspring, that person will be *homozygous* for the disorder—will have an identical pair of genes. Homozygotes always express the disease.

As many as 15 million Americans suffer from genetic disease. Over 3,500 established and 2,500 suspected disorders are hereditary. These are large figures; in fact, every family may include someone who is a potential victim of genetic disease or is susceptible to a disorder that may be linked to genetic causes, such as diabetes, cancer, or coronary artery disease. Genetic diseases account for over one-third of acute-care hospitalization of children under 18.

CASE 2: NANCY WEXLER AND TESTING FOR HUNTINGTON'S DISEASE

Clinical psychologist Nancy Wexler, born in 1945, graduated from Radcliff College in 1967. After a 10-year deterioration and catatonia, her mother died of Huntington's disease, a devastating, fatal neurological disease lacking cure or treatment. Because the Huntington's gene is dominant, Nancy and her sister Alice each had a 50 percent risk of inheriting the disease. Because the average age of onset is 36, victims usually have children before learning they are affected.

A severe, progressive neurological disease, Huntington's causes neurons in the caudate nuclei region of the brain to rapidly shed. Although age of onset varies, Huntington's is completely *penetrant* by age 65: the gene affects everyone with the disease.

Huntington's progresses through several stages (about five years each). First comes loss of muscular coordination and changes in personality, making victims angry, hostile, depressed, and sexually promiscuous. Next comes slurred speech, distorted facial expressions, constant muscular jerkiness, and staggering and falling. The third stage brings incontinence, dementia, and dependence on others, usually in an institution. In the last stage, victims are vegetative.

At present, 25,000 Americans have Huntington's, and about 100,000 Americans have an afflicted parent. Most victims are white. People at risk of Huntington's constantly wonder if each stumble augurs onset of the disease.

Unlike others at risk for genetic disease, Wexler helped both to discover the gene for Huntington's and to develop a predictive test for it. Around 1800, a European sailor with Huntington's jumped ship around Lake Maracaibo in Venezuela. He had 14 children, and because families there were large, by 1981 he had 3,000 descendants. Of these, 100 had Huntington's and another 1,100 were at risk. In 1981, Nancy led an expedition there to obtain blood samples from these descendants and to test them to find a genetic marker for Huntington's. Co-researcher James Gusella found such a marker in 1983.

In 1987, though the gene had not been discovered, Gusella developed a linkage test for Huntington's, meaning he could test for a batch of genes that included the Huntington's gene which tended to be inherited (or "linked") together. The linkage test allowed people such as Nancy to know odds about their risk, for example, 5 percent versus 80 percent. In this way, it prefigured today's genetic tests where people can know that they have an 80 percent risk of hereditary breast cancer or little risk, but do not get a simple yes-or-no answer.

In 1986, before the linkage tests, Nancy Wexler taught as a professor of clinical neuropsychology at Columbia University. She then said she would like to take the test when it became available. However, famously, she later changed her mind, deciding *not* to take the test.

The implications of her decision stunned people in medical genetics because a leading advocate for testing, who carried a 50 percent risk, had decided at the last minute to not know her risk. And she had spent a decade helping to develop this very test. Moreover, she was a clinical psychologist who should have known her own values.

Indeed, not only did Nancy not take the test, but over the next decades, she became an advocate for others not to take it. What was going on?

To people who want to be tested so that they could decide to go to law school, she said: "Go to law school! Develop your mind! What are you going to do if you're positive? Spend the rest of your life waiting to be a patient?"

In 1983, when James Gusella discovered the marker for Huntington's, he thought that finding the gene would take three to five years. In fact, it took *ten* years. Over the next decade, geneticists followed many false trails. Meanwhile, other researchers discovered single genes for muscular dystrophy, cystic fibrosis, neurofibromatosis ("elephant man" disease), colon cancer, ataxia, and sickle-cell anemia.

In 1993, an international team of six genetic laboratories discovered the exact molecular location of the Huntington's gene.[11] Now people could test directly for the gene, opening a new era in genetic testing. By 2007, Nancy Wexler had still not taken the test but frequently commented on genetic issues. Presumably, at age 62, she does not have the gene.

THE EUGENICS MOVEMENT

Before genetics became a science, a number of ill-founded ideas about heredity abounded. American pragmatist philosopher George Santayana famously said, "Those who cannot learn from history are doomed to repeat it." Knowing the

mistakes of the eugenics movement helps us to spot mistakes in public policy about today's genetics.

One mistake, *phrenology*, claimed that the inherited size and shape of the head determined intelligence and character. Although it seems ludicrous now, physicians then palpated the skull to assess character and IQ.

Other misconceptions stemmed from crackpot versions of Charles Darwin's theory of evolution by natural selection, especially his concept of "survival of the fittest." Darwin used fittest simply to mean "best adapted," so "fit" referred to the adaptation between an organism and its environment. Unfortunately, many people misunderstood "fit" to apply to social positions.

This misconception, *social Darwinism*, saw evolution in terms of group competition in human societies. Elitist, white social Darwinists held that social advantages implied biological superiority; therefore upper classes would prevail in any competition. They claimed that the fittest races would prevail in struggles for existence, so they predicted that blacks (whom they saw as biologically unfit) would not survive into the 20th century.

Social Darwinism can most charitably be described as unsophisticated. Not based on any understanding of evolution, it failed to take into account the vast numbers of organisms involved in attempts to survive, the enormous length of time over which these attempts evolve, or the ongoing role of adaptive mutations.

The *eugenics movement* flourished from 1905 to 1935 and hoped to improve hereditary characteristics through voluntary, selective breeding. Charles Darwin's cousin, Francis Galton, coined the term "eugenics" in the late 1880s.

Eugenics popped up worldwide: in Germany, Austria, Scandinavia, Italy, Japan, and South America, but as historian Daniel Kevles writes, "the center of this trend was the American eugenics movement. Its headquarters was at Cold Springs Harbor on Long Island, New York . . . ."[12] This point bears emphasizing: although many people identify modern eugenics with German Nazis, Americans—with their heterogeneous population—most passionately championed eugenics. American politicians, popular media, and scientists espoused it, advocated "eugenic marriages" and sterilization of the unfit, and declared that the American gene pool had declined through interbreeding with unfit races.

At the beginning of the 20th century in the United States, a few prominent families—largely of English, Swiss, German, and Dutch ancestry—exercised enormous wealth and power; they controlled many newspapers, magazines, and even universities, so they controlled many ideas of the time. These families obsessed about "breeding" and feared that the "purity" of Americans would be "contaminated" if their children bred with Irish, Italians, Turks, Jews, Asians, African-Americans, or anybody else whose origin differed from their own.

Wealthy and powerful families desired not only to preserve the purity of their own stock but also to control the growth of other groups. Watching the many progeny of Irish, Italian, and Greek immigrants, they saw Malthusian doom approaching. They thought the "unfit" had no right to bear children. A prominent New York urologist, William Robinson, proclaimed about people with mental retardation, "It is the acme of stupidity to talk in such cases of individual liberty, of the rights of the individual. Such individuals have no rights. They have no right in the first instance to be born, but having been born, they have no right to propagate their kind."[13]

Even on their own terms and in their own time, these ideas made little sense. Social Darwinism and eugenics contradicted each other: if the white race would emerge triumphant, why worry about excessive breeding among other races? If the lower classes were so "unfit" as to be destined to die out, why prevent them from breeding?

Eugenics enjoyed popularity because of a pervasive climate of bigotry (the same climate in Germany led to the rise of Hitler, anti-Semitism, and the Holocaust). The newspaper magnate William Hearst and Theodore Roosevelt thundered against "yellow niggers" who had invaded America from Asia. When Henry Ford ran for president in the 1920s, he promised to rid the country of the "Jew bankers," whom he accused of having caused America to enter World War I; later, he would accuse Jewish bankers of causing the Depression.[14]

The eugenics movement affected critical legislation in the United States. One kind of legislation permitted mandatory sterilization. While the Nazis famously sterilized 225,000 "mental defectives," the United States also practiced large-scale involuntary sterilization. In 1907, Indiana first required sterilization of the retarded and criminally insane; 30 other states soon followed. California led the nation in sterilizations, accounting for nearly a third of the national total; Virginia was second and Indiana third.[15] By 1941, physicians had sterilized over 36,000 Americans against their will, often for the vague condition of "feeblemindedness" or because victims had been born into large families on welfare. Some states did not reverse their sterilization laws until the 1960s.

The eugenics movement lay behind the famous (1927) *Buck* v. *Bell* decision by the United States Supreme Court. Supposedly retarded like her mother, Carrie Buck had been committed at age 18 to a state mental institution in Virginia. Pregnant when committed, Carrie gave birth to a daughter inside the institution.

Harry Laughlin, an influential geneticist who worked at Cold Springs Harbor, concluded that Carrie Buck's retardation was hereditary. He based this conclusion not on his own examination but upon reading a written report of a social worker, who said Carrie had a "feeble look" about her. Laughlin then declared that Carrie Buck "lived a life of immorality and prostitution," and that all the Bucks belonged to the "shiftless, ignorant, worthless class of anti-social whites of the South."

The U.S. Supreme Court upheld the legality of the Virginia law permitting Carrie Buck's sterilization. Justice Oliver Wendell Holmes wrote the majority (8 to 1) opinion:

> We have seen more than once that the public welfare may call upon the best citizens for their lives. It would be strange if it could not call upon those who already sap the strength of the State for these lesser sacrifices, often not felt to be such by those concerned, in order to prevent our being swamped with incompetence. It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes.

He concluded, "Three generations of imbeciles are enough."

The legal legacy of eugenics also included the *Immigration Restriction Act of 1924*. Hailed by eugenicists as their greatest triumph, it assumed the inferior genes

of Asians, Africans, Greeks, Irish, Poles, and Italians, and the superior genes of the English, Dutch, Scotch, Scandinavians, and Germans. President Calvin Coolidge enthusiastically signed the Act into law. As Vice President he said, "America must be kept American. Biological laws show . . . that Nordics deteriorate when mixed with other races.[16]

This Immigration Act established quotas according to countries of origin. Based on how many people from a given country were already in America, such quotas denied entry to people from "inferior" countries.

Indeed, America as a "melting pot" originally poured scorn on immigration. Similarly, the Statue of Liberty today symbolizes freedom, but after 1924, thousands of the world's "huddled masses" had only a glimpse of it before their boats were sent back.

In sum, eugenicists incorrectly assumed many things, among them:

1. *The reductionist assumption* that each trait identified by morality or social distinctions was caused by a gene in a one-to-one relation. Prostitution, retardation, poverty, and criminality were each supposedly caused by a single gene.
2. *The reductionist assumption* that genes cause diseases in a simplistic, one-gene-to-one-disease way. A few genetic diseases, such as Huntington's and sickle-cell, do work this way, but most do not.
3. *Ignorance about recessive inheritance.* Two unaffected carriers can each pass a gene for a recessive trait to a child, who will then be homozygous for the trait.
4. *Ignorance of environmental effects on expression of genes.* How a gene, or a combination of genes, is expressed depends in part on what happens during gestation, in early childhood, and in the overall environment. Genes have a fan-like range of expression (their norm of reaction), and which point on the fan manifests in a particular person depends on what happened in his or her environment.
5. *Naiveté as to the ease of controlling reproduction* in couples. Humans are driven to have sex, and if they aren't careful, children result. When informed of risk of a child with genetic disease, few humans can or will prevent birth of children, especially without access to contraception!
6. *Ignorance of mutations and chromosomal breakage.* Not knowing about these aspects of genetics, eugenicists mistakenly believed that if all retarded people could be prevented from reproducing, retardation could be eliminated from the gene pool.
7. *Ignorance of population genetics.* Eugenicists hoped to perfect humanity through selective breeding, but population genetics have since shown that there will be a regression to the mean. *Regression to the mean* is the inherent tendency in stable populations to return to an average value over time; in population genetics, the underlying causes creating a mean value in a population will eventually normalize any deviant values.

After 1935, the eugenics movement declined in the United States. Geneticist Hermann J. Muller said that eugenics was "hopelessly perverted," a cult for "advocates for race and class prejudice, defenders of vested interests of church and State, Fascists, Hitlerites, and reactionaries generally."[17] Another leading

geneticist, J. B. S. Haldane, said at the time of the sterilization programs that "many of the deeds done in America in the name of eugenics are about as much justified by science as were the proceedings of the Inquisition by the Gospels."[18] Advances in population genetics prompted Haldane to remark, "An ounce of algebra is worth a ton of verbal argument."[19]

The overall lesson of the eugenics movement is that politicians, educators, clergy, and some scientists hastily promoted laws and moral attitudes that had little to do with complex scientific facts. Paradoxically, the appeal of the solidity and inevitability of real, scientific facts gave plausibility to these nonfactual laws and attitudes. Unfortunately, many of the assumptions made were falsely reductionistic, based on ideology, or just plain wrong. If we call such laws and moral attitudes "public policy," then the eugenics movement showed that public policy can leap past verified facts in creating dangerous laws that harm people, all in the name of the very facts that are lacking.

CASE 3: GENES FOR BREAST CANCER

Like diabetes, breast cancer is more complicated than Huntington's. Most breast cancer is not caused by a single gene, has both preventive and curative treatments, and is not uniformly fatal.

Joan is a 50-year-old woman who had breast cancer at age 45 and had the affected breast removed, followed by radiation and chemotherapy and a maintenance course of tamoxifen. In high school and college, she smoked one to two packs of cigarettes a day, and for a decade in college and graduate school, used oral contraceptives. Cancer in females is associated with smoking and the pill, especially both together.

Joan blames herself for her cancer, but because her mother and aunt had breast cancer at the same age, wonders if she might have hereditary breast cancer. If she did, her daughters might take precautions. Moreover, if she did have the gene, her smoking and use of contraceptives might not have given her breast cancer.

Is most breast cancer caused by a gene? Despite the conventional wisdom, it is not. In fact, 95 percent of breast cancer is not caused by a gene. But the 5 percent that is caused by a gene is the center of controversy here.

In 1990, Mary Claire-King discovered a single gene, BRCA1 (BReast CAncer1) causing one form of breast cancer and ovarian cancer; its exact location was identified in 1994. Alan Ashworth in 1995 discovered another gene, BRCA2. In 2002, researchers discovered a third gene, CHEK2. Mutations in any of these genes cause breast cancer. Women in families expressing mutations in these BRCA1 or BRCA2 run an 80 percent risk of developing breast cancer in their lives, compared with a 9 percent risk for other women. Both BRCA1 and BRCA2 are autosomal dominant genes.

The science of presymptomatic testing for these genes is complex. Many mutations of BRCA1 and BRCA2 carry varying degrees of risk, which must be interpreted correctly for each family. The same mutation may act differently in different families or in twins with different lifestyles.

ETHICAL ISSUES

Testing as Self-Interest

Testing for genes for breast cancer may benefit the woman affected. Even with surgery, radiation, and chemotherapy for breast cancer, about 20 percent of women will still die from it. For this reason, significant percentages of women testing positive for breast cancer or for the genes BRCA1 or BRCA2 decided to remove both breasts in hopes of living to old age.

This is a significant ethical issue whose pedigree requires some explanation. In the 1960s, many women under 50 with breast cancer elected to have a bilateral mastectomy to remove both cancerous and precancerous tissue from their breasts.[20] In the 1970s and 1980s, studies showed that for most women with breast cancer, women getting a lumpectomy fared no worse than getting bilateral mastectomies. Because significant percentages of women experienced loss of femininity and self-esteem after their mastectomies, sparing them this surgery was thought to be a benefit.

However, the current views is that women with the breast cancer genes have an 80 percent chance of developing breast cancer during their lives, so for them bilateral mastectomy holds out a chance to prevent the cancer from starting at all.

Even before clinical trials finished, large numbers of women testing positive for BRCA1 and BRCA2 had preventive bilateral mastectomies. In 2002, a clinical trial proved that, five years after surgery, women with a BRCA1 or BRCA2 mutation undergoing prophylactic bilateral mastectomy have a statistically significant lower risk of breast cancer.

However, if there is any lesson in the ethics of genetic testing, it is that everything is complicated. Later studies suggested that the figure of 80 percent risk was exaggerated. Women with breast cancer initially recruited for studies of the two breast cancer genes came from families with breast cancer in grandmothers, mothers, daughters, and sisters, resulting in a selection bias.[21] So other women probably had their breasts removed based on data showing a much greater risk of breast cancer than they had.

Now add another twist. Besides the three mutations of BRCA1, BRCA2, and CHEK2 that cause breast cancer, hundreds of variant mutations now are known, each conferring a different degree of risk. Moreover, the risk of each variant may vary with the peculiarities of each family. Conveying all this information accurately requires sophistication by patient and genetic counselor.

But the history of genetics shows that sophistication and understanding of subtle, complex issues are not strengths of public policy or among the public. Women are likely to think "I have the breast cancer gene" and fear death in a few years from breast cancer.

If a woman has BRCA1, BRCA2 or CHEK2, the benefits of knowing early are that taking birth control pills reduces risk of ovarian cancer by 60 percent and taking the drug tamoxifen reduces risk of breast cancer by nearly half. More radically, prophylactic bilateral mastectomy increases longevity.

These same benefits apply to men, who account for about 2 percent of all cases of breast cancer.

Similarly, testing for the gene for type 2 diabetes could lead to benefits for Maria Lopez, especially if she could adopt a healthy lifestyle. For Maria and especially her daughters, it will be important to eat a low-fat, low-processed sugar diet and to exercise to keep their weight normal. In some cases, a positive test for the type 2 gene could be a wake-up call to adopt a healthy lifestyle.

Testing Only to Hear Good News

When people take genetic tests, do they really understand what they're doing? One Huntington's counselor says, "When people say they want this test to find out if they have the gene so they can make decisions, they really want to find out that they don't have it. The trouble is that fifty percent of them do. And there's no way to prepare them."[22]

In the first study of the linkage test for Huntington's, most people at risk (63–79 percent) originally said they would take the test, but some changed their minds later.[23] Some had expected to test negative and had intended to take the test to confirm this. This expectation indicated that they were in denial and were unprepared for a positive result; when they were well-counseled, counselors broke through their denial and they decided not to test.

The same study reported that "participants found to be probable gene carriers reported being surprised or shocked by the test result."[24] They had not expected to have the lethal gene.

Another consideration is that self-knowledge is seldom perfect. Many people simply cannot predict how they will react to testing positive—what they will feel or do if they learn the worst. Since Huntington's cannot be cured or ameliorated, a positive test will tell someone like Nancy Wexler that she is going to die an early, terrible death. Not everyone can deal with such knowledge. Moreover, isn't it inhumane to give people such a diagnosis when no treatment is possible? Perhaps people at risk of Huntington's should not be burdened with more truth than they can bear.[25]

On the positive side, testing for genes for breast cancer or diabetes allows intervention at an early stage. In one family, one of two sisters at hereditary risk worried about developing breast cancer and had planned to have her breasts removed as a preventive measure; she took the test for breast cancer genes, turned out to be negative and canceled her plan. Her sister did not think she was at risk and had refused mammograms but discovered she had the BRCA1 gene. A previous examination of her breasts had found nothing, but a reexamination found a minuscule node, and a biopsy determined that cancer had already begun, so a radical mastectomy was performed. Without the genetic test, this second sister might not have discovered her cancer until many years later.

Testing also allays fears of women who are "certain" they have such genes when they do not. Also, for some women, a mysterious, random turn of fate becomes testable and predictable. Although all women who test positive dislike the news, and although some who tested negative felt guilty, almost all think it's better to have a way to know.

Testing as a Duty to One's Family

Knowing one's likely genetic fate isn't just a concern of individuals. People are not atomistic; they come embedded in families, with children and parents, brothers and sisters.

The major argument favoring testing for serious genetic disease concerns childbearing. Nancy Wexler did not have children for fear that one might inherit Huntington's, yet perhaps her decision was misguided. If she had taken the test and been negative, she could have had children unaffected by Huntington's.

On the other hand, people who test positive should not have children or should test embryos and implant ones lacking the Huntington's gene. Why is that? Because parents should want the best lives for their children, and such lives start with freedom from genetic disease. No parent should willingly inflict a serious genetic disease on his or her child.

A second argument for testing concerns spouses and caretakers. Consider the following example. A man who was at risk for Huntington's but had decided not to take the test discussed his reasons before a large medical class. His reasons were greeted with respect; but as the class ended and the students started to file out, a woman cried out from the back of the room, "What about me and the kids? What about my view about testing him?" It was the man's wife.

She wanted to be able to plan for the future. If her husband were positive, she would be taking care of him. She might also have been thinking of money: if her husband were positive, he would eventually need custodial care, and they would have to start saving up for that or, if possible, arrange for life or health insurance. Moreover, when Huntington's strikes, the family as well as the victim will suffer emotionally; they should prepare themselves for this. Finally, they might try to make the most of whatever time remains before onset.

Besides a strict duty to one's family, compromises are possible. For instance, middle-aged people who do not want to know may feel that they have escaped the disease and that they can now take the test as a gift to their children. Another compromise is to have blood samples taken and stored at the International Research Roster for Huntington's in Indianapolis, Indiana, or at similar blood banks around North America. If someone dies before symptoms appear, his blood can be tested postmortem.

Testing One's Family by Testing Oneself

In any genetic testing, testing one family member has inevitable implications for other members of the family. In more ways than one, the results of testing affect the entire family.

Catherine Hayes gives an example:

> A case in point involves a pair of identical twins, only one of whom wanted to be tested. She swore that she would never reveal the results to anyone else in her family, in particular her twin. Once she was informed of the results—that there was a high probability that she would have Huntington's—the information spread quickly throughout the entire family. This meant that the twin who did not want to know her genetic status was now faced with the unwelcome knowledge that she too would probably have the disease.[26]

Hayes had five brothers and eight nieces and nephews. Though she tested negative, one of her brothers already has symptoms of Huntington's and another has tested positive; both already have children.

In one family where a woman tested for hereditary breast cancer, confidentiality was very difficult to maintain among the women of these extended families. It was hard for a woman to resist her family and not discover her status: in testing a middle-aged woman, one is also telling her mother and her daughters their risk of developing breast cancer.

It is important to keep in mind that in testing for dominant, single-gene diseases, such as Huntington's and the breast cancer genes, there is no such thing as testing only a fetus or testing only a parent: a positive fetus reveals a positive parent; a positive parent reveals that any children are at risk.

Helping families understand that genetic testing is difficult. Hayes notes, "Many medical professionals have difficulty viewing genetic issues in a family context. . . . Most researchers cannot possibly know what it is like to grow up in a family haunted by a genetic disease . . . ."

Testing may tear families apart. Consider the right to know. Even in a life-or-death situation, judges have ruled that relatives cannot be compelled to be tested for compatibility as bone-marrow or organ donors. Such decisions indicate that judges will not force genetic tests on relatives.

If a person tested positive for Huntington's and concealed it from a prospective spouse, could that be grounds for annulment? Does a prospective spouse have a right to know about such a test? Or does marrying "for better or worse" cover such questions?

Can one parent have a child tested in order to find out if the other parent is affected? Suppose that a father tests positive for Huntington's and refuses to tell his teenage daughter, Laura. Suppose that a genetic counselor is aware of the father's result. When Laura gets married, what should the counselor do? Recommend general genetic tests to her? Suppose she refuses. If she knew that her father was positive, would she agree to testing? If so, should the counselor violate the father's confidentiality? To many people, the good of preventing another child with Huntington's outweighs the harm of violating privacy, especially where there is a strong sense that the affected parent had an obligation to reveal his result in the first place.

One advocate for families afflicted with genetic disease believes that:

> first and foremost, genetic testing must be viewed as a family issue, not an individual one. The person who enrolls in a testing program should be strongly encouraged to involve other family members, within reason. Testing one member of a family will affect other members. Persons who refuse to involve their families may not have considered fully the consequences for other members or for themselves.[27]

Personal Responsibility for Disease

Let us return to the question of whether Joan and Maria are responsible for their diseases. The answer may be, "Yes and no." We can approach the question of responsibility in a less moralistic way by taking a different approach. Suppose

Joan and Maria each have three teenage daughters and that both Joan and Maria want to inoculate these daughters against a similar fate. The absolutely crucial question here is this: *Can these daughters avoid their mother's diseases?*

Put this way, we are not being moralistic or looking for a way to cast the first stone. Instead, we are doing preventive work, albeit in a conceptual way. "Conceptual" because we can assume ideal conditions: good education, maximal free will, good familial support for good eating, and so on. We can then ask, "Under ideal conditions, if they inherit their mother's genetic risk, can these daughters avoid breast cancer and diabetes?" Notice that this question has several dimensions: metaphysical (is there free will at all?), moral (are patients partly responsible for their diseases or good health?), and clinical (practically speaking, how much change can physicians expect of patients at-risk for breast cancer and diabetes?).

Type 2 diabetes is an especially good candidate for prevention because we know that many Asian people do not get diabetes until they adopt Western lifestyles. (Similarly, for Asian men immigrating to North American, incidence of prostate cancer jumps from 1 per 100,000 to 70 per 100,000.[28]) The prevailing view about preventing diabetes is this:

> What is especially disturbing about the rise of Type 2 [diabetes] is that it can be delayed and perhaps prevented with changes in diet and exercise. For although both types are believed to stem in part from genetic factors, Type 2 is also spurred by obesity and inactivity. This is particularly true in those prone to illness.[29]

So are 21 million Americans "failures" in personal responsibility because they have diabetes? Are another 10 million "successes" because they staved off genetic predisposition?

Let us take a larger perspective. Cancer occurs when tumor-suppressing genes or DNA repair mechanisms cease to work, resulting in wild, uncontrolled growth of cells. Diabetes occurs when the body fails to turn food into glucose, the body's chief source of energy.

Both diseases occur when environmental inputs trigger potential in an inherited genetic template. At the very least, avoidance of the inputs can delay onset of disease and perhaps avoid it altogether (people with genetic dispositions to alcoholism do not become alcoholics in countries where alcohol is banned). As a person ages, her immune system and organs deteriorate, and mutated cells in her body accumulate, making her more vulnerable to cancer and diabetes, so some people, despite healthy lifestyles, may eventually succumb to their genetic risk.[30]

Individuals and societies have some control over how many carcinogens are introduced to human bodies: tobacco sales can be banned in schools and hospitals, smoking can be forbidden in public, and people can avoid or quit tobacco. Similarly, junk foods and sodas can be banned from schools. Individuals at risk for cancer and diabetes can eat low-fat diets high in fiber, fresh fruits, and vegetables. In this way, both societies and individuals can reduce the likelihood of cancer and diabetes.

But what if a daughter gets cancer or diabetes anyway? Should she be blamed? Answer: probably not. To say that these diseases can be partially preventable by healthy living is not to say that some cases aren't, like Huntington's disease, genetically inevitable. Second, other factors in a person's life may have

prevented healthy living such that a person truly could not have done otherwise. In these cases, blame would be wrong.

Testing and Sick Identities

Nancy Wexler rejects an attitude she found dominant among the medical community about testing, which might be expressed as: "Come on! Take your knowledge like a man and don't be a sissy!" So everybody is expected to find out his or her genetic fate as soon as possible. The problem with this attitude is that it seems to benefit the medical community and family more than the individual affected. If there is no cure or treatment, as with Huntington's, what's so good about knowing?

Nancy Wexler thinks that people who test positive may adopt a "sick identity" for any genetic disease long before they experience any symptoms. That is one of her primary arguments against genetic testing. If you're going to get the disease, she argues, you will in fact get it, so there's nothing you can do about it. Why burden yourself being identified as "sick" long before you are?

Moreover, some people are highly suggestible. People who are concerned about suicide often focus on the consequences of testing teenagers—a population that is already highly suicidal. Youngsters who are merely at risk for Huntington's, breast cancer, or diabetes already agonize about going to college and spending their parents' money, and those who learn for certain that they have these genes may be even more vulnerable.

Should girls under 18 years of age be tested for these genes if they run in their families? At first glance, the answer seems no, for a positive answer might take away the fun of childhood and adolescence. Moreover, great danger exists of developing a sick identity as a "woman with breast cancer" or a "woman who will get diabetes." On the other hand, eating junk food and smoking start early in many teenagers, so early testing might be beneficial.

Preventing Suicide by Not Knowing

Because 25 percent of people with Huntington's consider suicide and 10 percent carry it out,[31] scientists have debated whether the test for Huntington's should be made available at all. Nancy Wexler said, "We have to understand that the day you tell someone he has this gene, his life and view of himself change forever. We're worried about the potential for suicide."[32] This argument might also be a factor, although to a lesser extent, in testing people for breast cancer or diabetes.

Should suicide be prevented at all costs, such that people who say they might commit suicide should not be tested for Huntington's? As Wexler emphasizes, "Huntington's patients know their family and they know what's happening to them. So in a way, it's worse than Alzheimer's."[33]

Is suicide an adequate reason for not testing? Even if 10 percent commit suicide, 90 percent do not. Nancy Wexler says, "Suicide is not unreasonable. It's not so awful that we can't discuss it or consider it." She observes, "For some of my friends who have Huntington's, knowing that they can commit suicide gives them a certain sense of control. They want to feel that if it gets too bad, they can have a way out. They can do something."[34]

Some scientists argue against paternalism: "I think we can trust people to make these decisions. I'm not so convinced we researchers should be dictating how the technology gets used."[35]

Testing Only with Good Counseling

Many people who are not absolutely opposed to testing—and even people who generally favor testing—argue that testing should only be offered *with good counseling*, especially because the results will be probabilistic for most people (not "You don't have the gene," but "You have a 90 percent chance of not having the gene").

This is, of course, paternalistic. However, it is true that some of those who test positive will wish they hadn't taken the test and some may develop emotional problems, and that counseling can help such people.

As a matter of public policy, should people, through their private physicians, simply be allowed to "buy" their own test results, or should counseling be required?

The President's Commission on Bioethics (1983) emphasized that counseling should be guaranteed: "A full range of prescreening and follow-up services . . . should be available before a program [of genetic testing] is introduced."[36] Note, though, that the recommendation here is for making counseling available, not mandatory.

This is not a realistic policy. First, 44 million Americans lack medical insurance and would need to buy genetic counseling, an expensive proposition. Second, just finding a trained genetics counselor is not easy, and many people do not live near a major medical center that has such a skilled counselor. Even for people with good medical coverage for physical illnesses, most policies today do not provide good coverage for genetic counseling.

Genetic Testing and Insurance

Genetic testing raises financial issues. For example, when one woman who tested positive decided to have a preventive radical mastectomy, she didn't want to tell her insurance company the reason for her decision because she was afraid her company would cancel her policy or raise her premiums, and perhaps even do the same for her daughters. Because her insurer didn't know anything, it thought she was being irrational and wouldn't pay for her surgery.

An important issue about genetic testing and medical insurance concerns confidentiality. Several national companies (such as Medical Information Bureau of Boston) inform insurance companies about applicants who are risks.[37] For people who take presymptomatic genetic tests and test positive, insurers could raise premiums for families. Worse, they could consider the result evidence of a preexisting condition and exclude that disease from future coverage.

For this reason, it is crucial to control the distribution of test results: that is, to decide who should and should not receive them. Many large institutions, such as the military, universities, and large companies, "self-insure" themselves and pass their losses along to employees through increased premiums. Moreover, some employers may not keep test results confidential, especially if key employees are involved; consequently, a positive result may keep an executive off the fast track.

Violation of confidentiality might also keep a physician out of a medical group, a student out of a university or graduate school, and so on.

Congress has considered a proposal, the Human Genome Privacy Bill, to ban insurers from access to genetic tests. A task force of the Human Genome Project has recommended that " . . . all individual risk information be excluded from decisions about who gets insured, what they get insured for, and how much they get charged. We see no other practical, sustainable plan for health care coverage than community rating."[38]

Genetic testing reveals the gaps in our national, medical *nonsystem*. If everyone who tests positive for genetic disease can get expensive medical coverage, while those who test negative are allowed to opt out, insurance companies will quickly go bankrupt. As genetic testing stresses our stopgap system, inequities of future health that it reveals may force us to adopt a national, single-payer system (for more on this, see the last chapter).

Genetic testing for diabetes exposes similar problems. Almost no money is spent by medical centers for education and counseling to prevent diabetes because doing so generally loses money. In contrast, waiting until crises develop and then amputating gangrenous legs produces profits (because insurance reimburses physicians well for doing surgical procedures, not for talking to patients).[39] Similarly, insurance companies curtail benefits to diabetics to discourage them from enrolling in their plans: "In a 2003 survey, 87 percent of health insurance actuaries . . . said that if they were to improve coverage [for diabetics] with richer drug benefits or easier access to specialists, they would incur financial problems by attracting the sickest, most expensive patients."[40]

Caveat Emptor: Making Money from Genetic Testing

In 2002, Myriad Genetics of Salt Lake City expanded its sales force from 85 to 600 agents to market BRCA1 testing directly to doctors and their patients. The tests, which cost between $750 and $2,750, would only benefit the 5 to 10 percent of people with breast cancer caused by these genes.

Unfortunately, BRCA1's discovery offered hope of a screening test only for women with hereditary breast and ovarian cancer—not for the 90 to 95 percent of women who develop nonhereditary breast cancer.

In some ways, marketing such tests is a win-win situation for Myriad Genetics. For the people who test positive, they get their money's worth and advance news. For the people who test negative, they get relief and will not complain about the money spent. The ethical issue arises when thousands of people seek relief who are really not at risk: they waste their money in getting a negative result. But it would be patronizing to say they can't spend their money as they choose, even irrationally.

Note that similar tests could be offered for genes for prostate cancer or diabetes, only a small percentage of which is caused by a single gene. For most people, such testing would be a waste of money.

Premature Announcements and Oversimplifications

Almost every week, the mass media report the discovery of a genetic basis for a disease or a trait (such as humor). Yet almost all such reports mislead us into

thinking that the genetic revolution has come. In fact, when we examine the practical aspects, in other words, when we look to see applications in ordinary medicine, we see the reality: progress is slow, hesitant, and results are usually complicated with many qualifications.

Recall that scientists created a linkage test in 1983 for Huntington's, predicted it would take 3 to 5 years to find the gene, and in fact, it took 10 years to find the gene. A good clinical test was not routinely offered until 1996. During the same decades, optimists predicted discovery of a gene for breast cancer, which finally came in 1994 and 1995, but practical tests for the three mutations took much longer. Scientists didn't discover a diabetes gene until 2000 and it took until 2006 to discover its exact location.

Just as the search for the these genes took longer and proved harder than expected, many early reports of discoveries of genetic causes of illnesses were premature. In 1987, researchers retracted an earlier claim that manic-depression was linked to a gene on the X chromosome.[41] By this time, earlier claims about genetic causes of schizophrenia and alcoholism had been retracted.

Today, geneticists believe that psychiatric disorders such as schizophrenia will not be found to be single-gene disorders. According to one leading researcher, common forms of mental illness may be caused by three to five genes acting together, probably with environmental co-factors.[42]

Like eugenics, much of the news about genetics in today's mass media is simplistic, alarmist, and premature. The movie *GATTACA* sums up these misconceptions, scaring us about imminent presymptomatic testing that may in fact be a century away.

Blame and Responsibility: Final Thoughts

Genetic testing may lead each of us to think more carefully about causes of gene-associated diseases. Presymptomatic testing may give some people a small window of preventive control. People at risk for cancers of the breast or prostate may be able to avoid smoking or being around second-hand smoke (exposure of children to the latter among smoking parents is strongly associated with later development of diabetes when children grow up[43]).

Previously, three standards of evidence were discussed that are used in the law: preponderance of evidence, clear and convincing evidence, and beyond a reasonable doubt. These standards can be used to make a point. We know beyond a reasonable doubt that no one with Huntington's disease can do anything to prevent this disease from destroying their brains and killing them. We also know that, for people with genes for breast cancer, unless they have double mastectomies, 80 percent of them will develop breast cancer.

This brings us to diabetes. Probably the best chance that prediabetics have to prevent diabetes is as children and adolescents, before they become overweight and have high levels of blood sugar. If they enter young adulthood overweight and accustomed to eating lots of processed sugars, the probability that they will develop diabetes is high.

Does that mean they should be blamed for their disease? No. To hand out blame, we would need to know, at least with clear and convincing evidence, that

they could have acted otherwise and eaten/exercised differently. It may be true that they could have, just as it may be true that the presumption of innocence allows some of the guilty to go free. But people who do not have genes for type 2 diabetes cannot really know what it's like to crave fats and sugars and to be tormented by these cravings. Yes, everyone is tempted, but some are tempted so much more intensely and continually than others! Until we have evidence that prediabetics could have acted otherwise, we should not blame them as individuals or in public policy.

That is compatible with educating young people and acting as if they can transcend their genetic dispositions. We want to think the best of people and to give them hope, but at the same time, we don't want to condemn them when they turn out to be less than ideal.

Finally, the history of eugenics shows that we almost always make huge mistakes in public policy about genetics, especially in oversimplifying complex issues. Responsibility may exist on a gradient, corresponding to a gradient of free will, such that some people have more than others. Two people with the same genes, placed at birth in different families (like Twain's *The Prince and the Pauper*) might as adults have differing degrees of free will and responsibility for their health or disease. On this perspective, poor people from dysfunctional families with no medical insurance, with genes predisposing them to diabetes or cancer, and little education will have less free will than well-educated young adults from loving, well-off families with good medical coverage who are blessed to have inherited good genes.

FURTHER READING AND RESOURCES

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Daniel Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity*, Knopf, New York, 1985.

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