GeNET. REPORT 4

HUMAN GENE

TESTING

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National Academy of Sciences Web Site

This article was adapted by science writer Margie Patlak from an article written by Howard Hughes Medical Investigator at Harvard University Stuart Orkin and National Institutes of Health scientist Gary Felsenfeld for ***Beyond Discovery™: The Path from Research to Human Benefit****, a project of the National Academy of Sciences. The Academy, located in Washington, D.C., is a society of distinguished scholars engaged in scientific and engineering research and dedicated to the use of science and technology for the public welfare. For over a century, it has provided independent, objective scientific advice to the nation.*

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Buried in the cells of each newborn is a unique set of genetic instructions. These molecular blueprints not only shape how the child will grow and develop and whether it will have brown eyes or blue, but what sorts of medical problems it might encounter. In some instances the likelihood of developing such disorders as heart disease or cancer can be forecast from a child's genes. How can doctors detect them in the morass of a person's DNA to try to prevent their deadly effects? The following article, adapted from an account by scientists Stuart Orkin and Gary Felsenfeld, explores the trail of research that led scientists to answer those questions and open the door to gene testing, which is promising to transform medicine powerfully. It provides a dramatic example of how science works and how basic research leads to practical results that were virtually unimaginable when the research was done.

Beth M.'s father died of colon cancer, as did his mother. Then colon cancer was diagnosed in two of her brothers, both in their 40s. Beth, 37, felt that a curse was hanging over her family and worried about her future and that of her children. Could she have inherited from her father a tendency to develop colon cancer at an early age, just as she inherited his hazel eyes?

Fortunately for Beth, researchers have pinpointed the defective gene that has plagued her family and causes the odds of developing colon cancer to be 85% or greater. The gene is called MSH2, and researchers have developed an experimental genetic test for defects in this particular gene. Within a short time of having her blood drawn, Beth could stop worrying--the blood test showed that she did not inherit the MSH2 gene from her father. Although the test result did not free Beth from the possibility of ever developing colon cancer--the test predicts only the likelihood of developing colon cancer fostered by the MSH2 gene, and not from other causes--she now knew that the uncomfortable and expensive colon-cancer detecting procedures that she underwent each year were no longer necessary; nor was the excessive worry.

What Beth didn't know was that the simple genetic test she had for the MSH2 gene would not have been possible without more than 50 years of research by many scientists who paved the way for pinpointing the genes that foster susceptibility to specific diseases. Most of the scientists had no idea that their quest for answers to such basic questions as how yeast cells detect and repair flaws in their genetic material would lead to practical genetic tests on people like the one for the MSH2 gene. These tests are also raising ethical, social, and legal questions as they take medicine into uncharted territory.

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Unraveling the Nature of the Gene:

A major milestone along the trail to gene testing was the discovery of the structure of deoxyribonucleic acid (DNA), the molecule that contains genes. It had been known since the middle of the 19th century, when the monk Gregor Mendel conducted his famous pea-breeding experiments, that physical traits such as height and color were passed from one generation to the next via units of inheritance that later came to be called genes. But the physical character of the gene had eluded scientists until 1944, when the studies of Oswald Avery, Colin MacLeod, and Maclyn McCarty of New York's Rockefeller Institute provided the first experimental evidence that DNA transmits genetic information. They showed that all that was needed to transform harmless bacteria into a type that can cause pneumonia was their uptake of DNA

from a pneumonia-causing strain of bacteria. That experiment suggested that genes were made of DNA, and it launched many researchers on a quest to determine the exact structure of DNA as a means of unraveling how genes exert their influence on all living things.

Two of these researchers, Rosalind Franklin and Maurice Wilkins, of King's College in London, studied the pattern generated when x-rays were scattered from DNA fibers. The photographic image immediately revealed that the DNA structure was regular and helical. With that information and knowledge of the chemistry of the DNA components, James Watson and Francis Crick, then at the Medical Research Council laboratories in Cambridge, England, began building molecular models that might account for the details in the photograph. The model that they ultimately proposed in 1953 contains two helically twisted strands connected to each other by a series of molecular "rungs." They suggested that each rung was composed of one of two chemical "base pairs" called adenine (A)-thymine (T) or guanine (G)-cytosine (C). These young scientists correctly surmised that it was the order of those A, T, G, and C bases on the DNA strand that spelled out the genetic endowment of every living organism. They also recognized that the two strands could be separated for copying--a simple mechanism for passing on genetic information from one generation to the next.

A few years after Watson and Crick clarified the structure of DNA, several other researchers, notably Marshall Nirenberg, at the National Institutes of Health, and Har Gobind Khorana, at the University of British Columbia, deciphered the genetic code that all living cells use to translate the series of bases in their DNA into instructions for the production of the thousands of proteins that determine the cell's structure and carry out all its functions, including determining such genetic traits as eye color and susceptibility to cancer. The researchers discovered that each triplet of bases (CTG, for example) codes for one amino acid (in this case leucine) or for a signal to start or stop building the long chain of amino acids that creates a protein.

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Genetic Errors Cause Disease:

The precise arrangement (sequence) of A, C, G, and T bases on a DNA strand is the recipe that encodes the exact sequence of a protein. If the recipes have extra bases or misspelled bases or if some are deleted, the cell can make a wrong protein or too much or too little of the right one. These mistakes often result in disease. In some cases, a single misplaced base is sufficient to cause a disease, such as sickle cell anemia.

Errors in our genes, our genetic material, are responsible for an estimated 3,000-4,000 hereditary diseases, including Huntington disease, cystic fibrosis, and Duchenne muscular dystrophy. What's more, altered genes are now known to play a part in cancer, heart disease, diabetes and many other common diseases. Genetic flaws increase a person's risk of developing these more common and complex disorders. The diseases themselves stem from interactions of such genetic predispositions and environmental factors, including diet and lifestyle. Some experts estimate that half of all people will develop a disease that has a genetic component.

Understanding the genetic code did not directly lead researchers to disease genes. Their ability to decipher the genetic messages encapsulated in DNA was stymied by the overwhelming number of such

messages carried in the DNA of each cell. A human cell (except sex cells--sperm and egg cells--and some blood cells that have no nuclei) contains about 6 feet of DNA molecules tightly coiled and packed into 46 chromosomes--rod-like structures in the cell nucleus that are formed from DNA covered with proteins. This DNA is made up of 3 billion base pairs. If printed out, those base pairs would fill more than 1,000 Manhattan telephone directories. When researchers tried to break up DNA molecules into more manageable pieces, however, they ended up with a chaos of random fragments whose order in the original DNA was lost.

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The Cutting Edge:

In the late 1960s, a useful molecular tool came to the rescue of these frustrated researchers, thanks to a series of studies by Werner Arber, in Switzerland, and Hamilton Smith, at Johns Hopkins University. These investigators were studying what at first seemed to be an unrelated problem. They were interested in understanding how some bacteria resist invasion by viruses. When viral DNA enters these bacteria, it is cut into small pieces and inactivated by enzymes called endonucleases. Smith showed that one of these enzymes cut the DNA at a specific short DNA sequence. Smith's colleague Daniel Nathans recognized that this provided a means of cutting a large DNA molecule into well-defined smaller fragments, and he used the method to generate the first physical map of a chromosome, that of the small monkey virus SV40. The map allowed Nathans to determine the arrangement of the individual genes within the DNA that forms the viral chromosome. With clairvoyance, Nathans speculated that larger chromosomes might be studied similarly. This heralded the mapping of chromosomes, an activity that forms the basis for the assignment of a disease gene to a specific region on a particular human chromosome.

The DNA cutting enzyme that Smith isolated was the first of over 1,000 "restriction enzymes" that have been discovered in just a few decades. Restriction enzymes not only allow chromosome mapping, they also enable researchers to generate large amounts of any specific DNA sequence of interest. These enzymes usually do not cut straight across the two strands of DNA, but cut in a staggered fashion. Consequently, their cuts create short, single-stranded tails on the ends of each fragment, called sticky ends. The sticky ends can be joined to other DNA strands with the aid of another type of enzyme, called ligase. By 1973, researchers were using restriction enzymes to cut specific DNA sequences of interest and join them to the DNA of bacteria. The bacteria then generated copies of the selected DNA with their own DNA each time they divided. Because a single bacterium grows rapidly, producing more than 1 billion copies of itself in 15 hours, large quantities of a specific DNA sequence can be produced in this manner--called cloning. This DNA can either be used for further study or to make DNA probes.

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Sifting Out Telltale Genetic Sequences:

The overwhelming number of genes in a human cell presented a major hurdle for researchers who wished to detect in a person's DNA a specific disease-fostering gene. For example, researchers wanted to detect the gene for the type of hemoglobin--the oxygen-carrying blood protein--that is absent in a severe form

of anemia, known as Cooley's anemia. This disease can cause such debilitating illness or even death at an early age that scientists wanted to devise a way to detect it before birth.

Researchers had used the genetic code to determine the DNA sequence that codes for the series of amino acids that make up part of the hemoglobin protein. But they had no means of sifting the telltale DNA out of the DNA of the 100,000 other genes in a human cell, so that they could tell whether the gene was normal or not.

A way around the problem was discovered in 1975 when a Scottish scientist, Edward Southern, developed a powerful method to pinpoint a specific genetic sequence. Restriction enzymes were used to cut DNA into fragments, which were then separated by size by being sifted through a porous jelly-like substance through which an electric current is passed. The smaller fragments move faster through the gel than the larger ones, so that the DNA fragments from different genes end up at different positions. Then the separated fragments are blotted out of the gel onto a sheet of paper without changing their relative positions, and the paper copy of the gel is bathed in a solution containing radioactive DNA molecules, called probes. These probes are cloned DNA fragments with sequences that match a DNA sequence in the gene of interest (for example, the hemoglobin gene). Matching means that an A on one strand of the probe is matched by a T on a strand from the gene, a G is matched by a C, and so on for long distances along the two DNA molecules. This allows the DNA probe and the DNA fragment that is stuck to the paper to pair, making that region of the paper radioactive.

Because the probes are radioactive where they bind to the paper, they give off signals that can be made visible on x-ray film. This simple method, named Southern blotting after its creator, allowed researchers to detect a single DNA fragment from the hemoglobin gene among more than 100,000 other fragments in the same gel. Shortly after Southern blotting was developed, researchers used it to develop a prenatal test for Cooley's anemia and other rare conditions for which telltale DNA sequences were known.

A serendipitous observation in 1978 by researchers at the University of California, San Francisco, made Southern blotting useful in the detection of several more common disorders. Yuet Wai Kan and Andree-Marie Dozy were studying patients with sickle-cell anemia, a hereditary disease in which a single change in DNA gives rise to a defective form of hemoglobin that fosters painful and sometimes fatal blood clots. The researchers noticed, after they used a restriction enzyme to cut the DNA of patients with sickle-cell anemia, that most of the patients had a DNA fragment containing the beta-hemoglobin gene that was 13,000 base pairs long. People without sickle-cell anemia often lacked this particular DNA fragment after their DNA was cut by the same enzyme. Because the fragment produced was different in size from that normally seen, it was called a restriction-fragment-length polymorphism (RFLP).

RFLPs have been found in association with many common genetic disorders, including Huntington disease and some kinds of cancers. The RFLPs allow scientists to use Southern blotting to detect a disease or disease susceptibility in a person without knowing the precise DNA sequence of the gene that fosters it. RFLPs are used in a second way. An RFLP that is tightly linked to a specific disease (that is, where people who have the disease almost always have the specific RFLP) lies near the sequence of DNA that houses the disease-fostering gene. Therefore, by finding the cutting site on the DNA that created the RFLP, the disease gene itself can eventually be isolated.

The search for RFLPs linked to specific disorders can sometimes be narrowed to a specific region of a chromosome with the aid of chromosomal staining. Developed in the 1970s, chromosomal stains reveal a

pattern of light and dark bands that reflects regional variations in the amounts of A and T bases versus G and C bases. Under a light microscope, differences in size and banding pattern distinguish the 23 chromosome pairs from each other and reveal major chromosomal abnormalities, including missing, added, or misplaced pieces of chromosomes. The eye cancer retinoblastoma, for example, often is associated with a missing band on chromosome 13; this finding led researchers to look for retinoblastoma-associated RFLPs within that region of the chromosome.

Researchers can also track a specific RFLP to a section of a particular chromosome by tagging it with an observable label (one that is fluorescent or radioactive). The location of the labeled RFLP can be detected after it binds to its complementary sequence of bases in an intact chromosome. This technique is known as in situ hybridization.

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Spelling Out Disease Genes:

To improve the precision of gene testing, scientists needed to spell out the actual DNA sequence of disease-fostering genes (the order of the A, C, G, and Ts). This endeavor was greatly aided by the development of a method for rapidly sequencing DNA by Harvard University researchers in 1977. One of the researchers, Walter Gilbert, had been trying to understand how particular genes in bacteria were turned off (prevented from generating the proteins for which they code) and he saw that he would not make much headway unless he could determine the sequence of particular segments of the bacterial DNA. He then worked with his colleague Allan Maxam to concoct a novel method that combines chemicals that cut DNA only at specific bases with radioactive labeling and Southern blotting to determine quickly the precise sequence of long DNA segments. A different but equally successful DNA sequencing method was developed at about the same time by Fred Sanger in Cambridge, England.

In the early 1980s, the Maxam-Gilbert and Sanger methods for DNA sequencing were improved and automated to speed the process. The pinpointing of disease-fostering genes could now proceed relatively quickly. Using a technique called positional cloning, researchers first zero in on the chromosome likely to house a disease gene by using chromosomal staining, in situ hybridization, or other techniques. Once the chromosomal home of the disease gene has been identified, they look for RFLPs or other genetic markers in that location that are tightly linked to the disease. They then determine the sequence of the DNA bases in the region of the telltale markers. They know that their search is over if they pinpoint a DNA sequence that is found only in people with the disease in question. Positional cloning has thus far been used to find over 50 disease genes, including the gene for cystic fibrosis, Duchenne muscular dystrophy, some types of Alzheimer's disease, and early-onset breast cancer.

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Revolutionary Copying Technique Developed:

Genetic tests for the disorders caused by disease genes could not make it from the laboratory bench to the doctor's office until researchers developed an easy and inexpensive way to copy specific DNA

molecules. That way, the small amount of DNA extracted from a person's blood or tissue sample could be multiplied into the large quantities needed for DNA sequencing.

Once again, scientists doing basic research overcame a stumbling block. In a small California biotechnology company, the Cetus Corporation, a young scientist, Kary Mullis, was employed to generate new ideas instead of doing bench experiments. He recognized that rather than relying on bacteria to duplicate selected DNA in a cloning process, he could use just the enzymes--called DNA polymerases--that bacteria themselves use to copy DNA. He developed a method, called the polymerase chain reaction and abbreviated as PCR, that allows the enzymes to be used to amplify any specific DNA sequence in a test tube.

There was only one catch--the method worked only on single-stranded DNA and the heating that is needed to unzip the two strands of DNA kills the polymerases. Fortunately, researchers several years earlier had isolated bacteria that had the amazing ability to thrive at temperatures near that of boiling water in hot springs. Scientists discovered that the polymerase isolated from these bacteria could survive the high temperatures needed for PCR. By the late 1980s, the PCR technique had spawned a number of practical developments, of which gene testing is only one.

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Tracking a Colon-Cancer Gene:

By 1990, researchers had the techniques that they needed to search for the gene that causes an important form of colon cancer known as hereditary nonpolyposis colorectal cancer (HNPCC). People who inherit the HNPCC gene have an 80% or greater chance of developing colon cancer and other cancers, usually at an early age. Women with the gene also face a markedly increased risk of uterine and ovarian cancer.

The search for the HNPCC gene had actually begun more than 30 years earlier in the laboratories of several scientists who were working on bacteria and yeast to learn what happens to the occasional genetic errors that occur during sexual reproduction or when DNA is damaged by particular chemicals. These errors stem from DNA that has incorrectly paired bases (an A paired with a G, for example, instead of with a T). Studies showed that bacterial and yeast cells had a way of snipping out the mismatched bases in a process called mismatch repair. Through genetic analysis in both bacteria and yeast, several genes critical to the mismatch pathway were identified and their protein products were characterized.

Paul Modrich had devoted much of his academic career to working out the details of this repair mechanism in bacteria. By 1992, Richard Kolodner and his colleagues at the Dana Farber Cancer Institute in Boston had isolated a gene called Mut S homolog 2 (MSH2), which was needed for mismatch repair in yeast. Kolodner speculated that people probably also had a similar gene that governed mismatch repair. Because the process is vital to the functioning of cells, Kolodner assumed that errors in a human version of MSH2 and other mismatch-repair genes would cause some human diseases. With that in mind, he and his collaborators used PCR to detect the human MSH2 gene at the end of 1993.

Meanwhile, Bert Vogelstein at Johns Hopkins University and his colleagues in Finland were studying the families of people afflicted with HNPCC. They had used positional cloning to pinpoint the gene for the

condition and published its sequence two weeks after Kolodner and his collaborators had published the sequence of their human MSH2 gene. The two sequences were identical: Vogelstein's disease gene for HNPCC was the same as Kolodner's MSH2 gene. Shortly after, a second mismatch-repair gene was found also to cause HNPCC. Vogelstein, Kolodner, and other researchers have since developed genetic tests for these two genes. The tests can tell people, in families prone to HNPCC, whether they have one of the genes that foster it. As many as 1 in 200, or 1.25 million Americans, may carry one or the other of these altered genes. People found to carry an altered gene can be counseled to adopt a high-fiber, low-fat diet in the hope of preventing cancer. They can also be advised to start yearly colon examinations at about age 30. Such examinations should help physicians to detect any precancerous growths on the colon so that they can remove them before the growths turn malignant. For those people, like Beth, who turn out not to carry the altered genes, the diagnostic test can provide a huge relief, removing the fear they have lived under as well as the need for frequent colon examinations.

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Medicine Transformed:

The HNPCC gene-test story is just one of many that illustrate how gene testing is dramatically transforming the practice of medicine. This new ability to probe genes, however, can be a double-edged sword. For some diseases, such as Alzheimer's disease, the ability to detect a faulty gene has outpaced medical science's ability to do anything about the disease that it causes. The possibility of genetic testing for these diseases raises a number of controversial social issues that scientists alone cannot resolve. Policy-makers, lawyers, and scientists are working hard to come up with answers to the many novel social questions that gene testing poses. (See the next section.)

But for many disorders, by genetically forecasting a person's likelihood of developing a disease long before symptoms appear, doctors have a much better chance to prevent the disorder or to detect it at its earliest stages when treatment is more likely to be successful. A newborn who tested positive in a genetic test for retinoblastoma, for example, was screened for eye tumors just a few weeks after he was born. His doctor discovered that he had two tumors in each eye, and was able to save the infant's sight by treating him with radiation.

In addition, prenatal genetic testing for fatal or extremely debilitating conditions is reducing their incidence in the general population. A prenatal screening program for the severe form of anemia known as beta-thalassemia, for example, led to the near eradication of this deadly disease on the Italian island of Sardinia. A twenty-fold reduction in the incidence of the fatal neurologic disorder Tay-Sachs disease occurred in the Baltimore area following the development and implementation of a prenatal screening program for the Tay-Sachs gene. For parents who choose to carry to full term a fetus with a debilitating genetic disorder, prenatal testing allows preparation for the medical care that their children will need.

In the long run, the deciphering of the genetics of human disorders is likely to lead to better treatments. Shortly after the genes for cystic fibrosis and Duchenne muscular dystrophy were discovered, for example, researchers developed experimental treatments for these disorders that aim to correct or replace the faulty genes responsible for them. Drugs that can alter or replace the protein gene products that are missing or defective in some cancers and other disorders also are being pursued.

None of those medical feats would have been possible if researchers had not been able to pursue their curiosity about such basic riddles as what governs a pea plant's height, or how genes are passed from one bacterium to another. Many of the scientific breakthroughs that led to gene testing stemmed from serendipitous findings in totally unrelated studies and from basic research, much of it publicly funded, whose far-flung practical implications were completely unexpected by their discoverers--curious people who just wanted to understand how nature works.

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Gene Testing Poses Social Dilemmas:

Unfortunately, people with many diseases, such as Huntington disease, will initially find that their disease is predictable through gene testing, but not yet preventable or curable. Gene testing in those cases poses a number of ethical, psychological, and legal dilemmas. Recent federal legislation reduces the concern that people might be denied insurance or employment solely because they test positive for some condition. Several states have passed laws that prohibit insurance discrimination based on the results of gene tests. But the emotional distress that testing positive can promote is also an important concern.

Lawmakers, policymakers, and scientists are exploring ways to address some of the societal implications of gene testing. A 1994 Institute of Medicine report suggested a number of guidelines for genetic screening. These include extensive education and counseling of people receiving gene tests as well as the reservation of widespread genetic testing for treatable or preventable conditions of relatively high frequency. The Human Genome Project, whose goal is to sequence all the genes in human DNA, supports research aimed at developing policies or programs that maximize the benefits of genetic research while minimizing the potential for social, economic, or psychological harm. As genetic forecasting takes medicine to new heights, it forces the legal, ethical, and social policies that guide its usefulness to advance to new heights of sophistication as well.

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Advances in Genetic Research That Led to Gene Testing:

This timeline shows the chain of research events that led to the gene testing that predicts the likelihood of developing various diseases. It is rich in examples of the contributions of basic research to unexpected outcomes of immense societal benefit.

1860-1865
Gregor Mendel conducts his pea-breeding experiments that show how physical traits, such as height and color, are passed from one generation to the next through genes.

1944
The studies of Oswald Avery and Colin MacLeod provided the first experimental evidence that DNA

transmits genetic information.

1953
Using an x-ray pattern of DNA generated by Rosalind Franklin Maurice Wilkins, James Watson and Francis Crick publish their double-helix model DNA. This accurately predicts the order of repeating molecules, known as bases, on the DNA strand spells out the genetic endowment of every living organism.

1960-1966
Marshall Nirenberg, Har Gobind Khorana, and their colleagues decipher the genetic code that all living cells use to translate the series of bases in their DNA into instructions for the production of proteins.

1970
Hamilton Smith discovers the first restriction enzyme that cuts DNA at specific sites. Daniel Nathans uses such restriction enzymes to generate the first physical map of a chromosome.

1973
Researchers begin to use genetically altered bacteria to clone DNA sequences.

1975
Edward Southern develops a method, known as Southern blotting, to pinpoint a specific genetic sequence.

1977
Walter Gilbert and Allan Maxam, and Fred Sanger working separately, develop techniques for rapidly "spelling out" long sections of DNA by determining the sequence of bases.

1978
Yuet Wai Kan and Andree-Marie Dozy discover restriction-fragment-length polymorphisms (RFLPs).

1985-1990
Kary Mullis and his colleagues develop a technique, called the polymerase chain reaction (PCR), for quickly amplifying and thereby detecting a specific DNA sequence.

1986
The first disease gene detected by positional cloning is identified, that for an immune disorder called chronic granulomatous disease.

1992
Building on work of Paul Modrich on understanding the DNA mismatch repair mechanisms in bacteria, Richard Kolodner and colleagues isolate a gene called MSH2 that functions in yeast mismatch repair.

1993
Bert Volgelstein and Kolodner discover that defects in the human MSH2 gene are responsible for hereditary nonpolyposis colorectal cancer (HNPCC).

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Understanding Gene Testing

Introduction:

Genes - the chemical messages of heredity - constitute a blueprint of our possibilities and limitations. The legacy of generations of ancestors, our genes carry the key to our similarities and our uniqueness.

When genes are working properly, our bodies develop and function smoothly. But should a single gene - even a tiny segment of a single gene - go awry, the effect can be dramatic: deformities and disease, even death.

In the past 20 years, amazing new techniques have allowed scientists to learn a great deal about how genes work and how genes are linked to disease. Increasingly, researchers are able to identify mutations, changes within genes that can lead to specific disorders. Tests for gene mutations make it possible not only to detect diseases already in progress but also, in certain situations, to foresee diseases yet to come.

This new ability raises both high hopes and grave concerns. On the one hand, predictive gene testing holds out the possibility of saving thousands of lives through prevention or early detection. On the other, the implications of test results are enormous, not only for the individual but also for relatives who share this genetic legacy, and for society as a whole.

DNA, which carries the instructions that allow cells to make proteins, is made up of four chemical bases. Tightly coiled strands of DNA are packaged in units called chromosomes, housed in the cell's nucleus. Working subunits of DNA are known as genes.

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What are genes?

Genes are working subunits of DNA. DNA is a vast chemical information database that carries the complete set of instructions for making all the proteins a cell will ever need. Each gene contains a particular set of instructions, usually coding for a particular protein.

DNA exists as two long, paired strands spiraled into the famous double helix. Each strand is made up of millions of chemical building blocks called bases. While there are only four different chemical bases in DNA (adenine, thymine, cytosine, and guanine), the order in which the bases occur determines the information available, much as specific letters of the alphabet combine to form words and sentences.

DNA resides in the core, or nucleus, of each of the body's trillions of cells. Every human cell (with the exception of mature red blood cells, which have no nucleus) contains the same DNA. Each cell has 46 molecules of double-stranded DNA. Each molecule is made up of 50 to 250 million bases housed in a chromosome.

The DNA in each chromosome constitutes many genes (as well as vast stretches of noncoding DNA, the function of which is unknown). A gene is any given segment along the DNA that encodes instructions that allow a cell to produce a specific product - typically, a protein such as an enzyme - that initiates one specific action. There are between 50,000 and 100,000 genes, and every gene is made up of thousands, even hundreds of thousands, of chemical bases.

Human cells contain two sets of chromosomes, one set inherited from the mother and one from the father. (Mature sperm and egg cells carry a single set of chromosomes.) Each set has 23 single chromosomes - 22 autosomes and an X or Y sex chromosome. (Females inherit an X from each parent, while males get an X from the mother and a Y from the father.)

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How do genes work?

Although each cell contains a full complement of DNA, cells use genes selectively. Some genes enable cells to make proteins needed for basic functions; dubbed housekeeping genes, they are active in many types of cells. Other genes, however, are inactive most of the time. Some genes play a role in early development of the embryo and are then shut down forever. Many genes encode proteins that are unique to a particular kind of cell and that give the cell its character - making a brain cell, say, different from a bone cell. A normal cell activates just the genes it needs at the moment and actively suppresses the rest.

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How are genes linked to disease?

Many, if not most, diseases have their roots in our genes. Genes - through the proteins they encode - determine how efficiently we process foods, how effectively we detoxify poisons, and how vigorously we respond to infections. More than 4,000 diseases are thought to stem from mutated genes inherited from one's mother and/or father. Common disorders such as heart disease and most cancers arise from a complex interplay among multiple genes and between genes and factors in the environment.

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How does a faulty gene trigger disease?

A sound body depends on the continuous interplay of thousands of proteins, acting together in just the right amounts and in just the right places - and each properly functioning protein is the product of an intact gene. Genes can be altered (mutated) in many ways. The most common gene mistake involves a single changed base in the DNA - a misspelling. Other alterations include the loss or gain of a base. Sometimes long segments of DNA are multiplied or disappear.

Some mutations are silent; they affect neither the structure of the encoded protein nor its function. Other mutations result in an altered protein. In some instances, the protein is normal enough to function, but not

well; this is the case of the flawed hemoglobin the oxygen-carrying protein in the blood that causes sickle-cell anemia. In other instances, the protein can be totally disabled. The outcome of a particular mutation depends not only on how it alters a protein's function but also on how vital that particular protein is to survival.

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How do gene mistakes occur?

Gene mutations can be either inherited from a parent or acquired. A hereditary mutation is a mistake that is present in the DNA of virtually all body cells. Hereditary mutations are also called germline mutations because the gene change exists in the reproductive cells (germ cells) and can be passed from generation to generation, from parent to newborn. Moreover, the mutation is copied every time body cells divide.

Acquired mutations, also known as somatic mutations, are changes in DNA that develop throughout a person's life. In contrast to hereditary mutations, somatic mutations arise in the DNA of individual cells; the genetic errors are passed only to direct descendants of those cells. Mutations are often the result of errors that crop up during cell division, when the cell is making a copy of itself and dividing into two. Acquired mutations can also be the byproducts of environmental stresses such as radiation or toxins.

Mutations occur all the time in every cell in the body. Each cell, however, has the remarkable ability to recognize mistakes and fix them before it passes them along to its descendants. But a cell's DNA repair mechanisms can fail, or be overwhelmed, or become less efficient with age. Over time, mistakes can accumulate.

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How does heredity influence disease?

Genes come in pairs, with one copy inherited from each parent. Many genes come in a number of variant forms, known as alleles. A dominant allele prevails over a normal allele. A recessive gene becomes apparent if its counterpart allele on the other chromosome becomes inactivated or lost.

For example, in cystic fibrosis (a disease that seriously impairs breathing and digestion), the gene that causes abnormal mucus production and disease is a recessive allele. A person who inherits one copy of the recessive allele does not develop disease because the normal allele predominates. However, such a person is a carrier who has a 50-50 chance of passing the altered recessive allele to each of his or her descendants. When both parents are carriers, the chance is one in four that a child will inherit two of the recessive alleles, one from each parent, and develop disease. (This chance remains one in four for each pregnancy.) Although most recessive mutations are rare, a few, including those for cystic fibrosis and sickle-cell anemia, are fairly common in specific ethnic groups.

However, most diseases and traits don't follow simple patterns of inheritance; a variety of factors influence a gene's performance. To begin with, not all mutated alleles invariably lead to disease. Even with a dominant allele such as the BRCA1 breast cancer susceptibility gene, for instance, the risk of

disease by age 65 is 80 percent, not 100 percent. This quality - an indication of the probability that a given gene mutation will produce disease - is referred to as penetrance.

Not only can different mutations in the same gene produce a wide range of effects in different individuals, as is the case with cystic fibrosis, but also mutations in several different genes can lead to the identical outcome, as is the case with some forms of Alzheimer's disease. Some traits require simultaneous mutations in two or more genes. And a phenomenon known as imprinting can determine which of a pair of genes, the mother's allele or the father's, will be active or silenced.

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What is gene testing?

Gene testing involves examining a person's DNA - taken from cells in a sample of blood or, occasionally, from other body fluids or tissues - for some anomaly that flags a disease or disorder. The DNA change can be relatively large: a missing or added piece of a chromosome - even an entire chromosome - that is visible under a microscope. Or it can be extremely small, as little as one extra, missing, or altered chemical base. Genes can be over expressed (too many copies), inactivated, or lost altogether. Sometimes, pieces of chromosomes become switched, or transposed, so that a gene ends up in a location where it is permanently and inappropriately turned on or off.

In addition to studying chromosomes or genes, genetic testing in a broader sense includes biochemical tests for the presence or absence of key proteins that signal aberrant genes.

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What are the uses of genetic testing?

Genetic tests can be used to look for possible predisposition to disease as well as to confirm a suspected mutation in an individual or family.

The most widespread type of genetic testing is newborn screening. Each year in the United States, four million newborn infants have blood samples tested for abnormal or missing gene products. Some tests look for abnormal arrangements of the chemical bases in the gene itself, while other tests detect inborn errors of metabolism (for example, phenylketonuria) by verifying the absence of a protein that the cell needs to function normally.

Carrier testing can be used to help couples to learn if they carry - and thus risk passing to their children - a recessive allele for inherited disorders such as cystic fibrosis, sickle-cell anemia, or Tay-Sachs disease (a lethal disorder of lipid metabolism). Genetic tests - biochemical, chromosomal, and DNA-based - also are widely available for the prenatal diagnosis of conditions such as Down syndrome.

In clinical research programs, doctors make use of genetic tests to identify telltale DNA changes in cancer or precancer cells. Such tests can be helpful in several areas: early detection (familial adenomatous polyposis genes prompt close surveillance for colon cancer); diagnosis (different types of

leukemia can be distinguished); prognosis (the product of a mutated p53 tumor-suppressor gene flags cancers that are likely to grow aggressively); and treatment (antibodies block a gene product that promotes the growth of breast cancer).

Much of the current excitement in gene testing, however, centers on predictive gene testing: tests that identify people who are at risk of getting a disease, before any symptoms appear. Tests are already available in research programs for some two dozen such diseases, and as more disease genes are discovered, more gene tests can be expected.

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How are disease genes identified?

Tracking down every chemical base in each of the estimated 50,000 to 100,000 genes as well as the spaces between them - mapping the human genome - is the task of an international 15-year collaboration known as the Human Genome Project. (The United States effort is shared by the National Center for Human Genome Research at the National Institutes of Health and the Office of Health and Environmental Research of the Department of Energy.) Scientists expect that having a detailed map of the entire set of human genes will revolutionize medical practice and biomedical research.

The Human Genome Project is focusing on the creation of genome maps, both genetic linkage maps and physical maps. Genome maps depict the order in which genes, genetic markers, and other landmarks are found along the chromosomes.

In narrowing the search for a specific gene, researchers often identify gene markers - characteristic segments of DNA or genes for known traits - that lie close to the target gene and are inherited along with it.

Genetic linkage maps assign chromosomal locations to genetic landmarks - either genes or distinct short sequences of DNA - on the basis of how frequently markers are inherited together. Linkage maps exploit a phenomenon called recombination or crossing over. As developing sperm and egg cells divide, pairs of maternal and paternal chromosomes sometimes break and exchange pieces with one another. Genes and markers that are physically close to one another on the chromosome are said to be tightly linked; they are much less likely to be separated by recombination than are gene markers that are located far apart. In 1994, international collaborators published a comprehensive linkage map charting more than 5,000 markers and more than 400 genes.

After scientists use genetic linkage maps to assign a gene to a relatively small area on a chromosome, they next examine the region up close to learn the gene's precise location. To do this, scientists turn to physical maps.

To construct a physical map, a chromosome (or in some cases, the whole genome) is first broken into smaller pieces of DNA. Scientists then copy or clone the pieces in the laboratory, obtaining millions of identical copies of specific DNA segments. They next line up the clones to reflect the order that existed on the original chromosome. Information about the location and known genetic content of these unique and ordered DNA fragments (called contigs) is stored in a computer, while clones of the ordered pieces

themselves are stored in laboratory freezers. When genetic linkage maps indicate that a gene lies in a particular region, scientists can go to the freezer and retrieve clones of interest; they then use the clones as the raw material for DNA sequencing - actually identifying the order of each and every chemical base in the gene.

Benefiting from the increasingly detailed maps and sophisticated DNA sequencing techniques and tools, scientists are mapping and isolating new disease genes at the rate of several per month. By the year 2005, scientists hope to pinpoint the location of each of the 50,000 to 100,000 genes and to identify the exact sequence of their chemical bases.

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What types of diseases can be predicted with gene tests?

Predictive gene tests look for disorders that "run in families" as the result of a faulty gene that is inherited.

When a mutated gene is inherited because it was carried in the reproductive cells (egg or sperm), the mutation will be present in cells throughout the body. This means that the mutation can be detected in white blood cells in a blood sample, for instance.

Predictive gene tests are presently available for diseases such as Tay-Sachs disease and cystic fibrosis, and tests are being developed for many more conditions, including a predisposition to ALS, or amyotrophic lateral sclerosis, the fatal nerve degeneration known as Lou Gehrig's disease; Huntington's disease, a devastating disorder of middle age that causes dementia and ends in death; some forms of Alzheimer's disease; and catastrophically high cholesterol.

Genes have also been found for several types of cancer that can run in families.

Several of these are rare conditions that affect only a few people: a childhood eye cancer known as retinoblastoma; Wilms' tumor, a kidney cancer that usually appears before age 5; and the Li-Fraumeni syndrome, in which children and young adults of the family develop an assortment of cancers, including sarcomas in the bones and soft tissues of the arms and legs, brain tumors, acute leukemia, and breast cancer. In 1993, scientists identified the gene that causes familial adenomatous polyposis, an inherited predisposition to form precancerous polyps. This condition is believed to be responsible for about 1 percent of colon cancers.

More recently, scientists have identified gene mutations that are linked to inherited tendencies toward common cancers, including colon cancer and breast cancer. Families who carry these altered genes may also have an increased risk of other cancers. Women with an altered copy of the BRCA1 breast cancer susceptibility gene, in particular, are susceptible to ovarian cancer as well. People who inherit cancer genes are more likely to develop cancer at a young age, because the predisposing gene damage is present throughout their lives, ready to set cancer's uncontrolled growth in motion should the normal allele be lost or inactivated.

Such inherited, or familial, forms of cancer represent perhaps about 5 to 10 percent of all cancers. The great majority of people who get breast cancer or colon cancer have not inherited such highly active altered genes. This is true even for many families that have several members with cancer; certain cancers are so common that some clusters are bound to happen purely by chance. Cases that are diagnosed at older ages, in particular, are more likely to be caused by acquired mutations.

Nevertheless, because breast and colon cancer are so widespread, even a small fraction of the total equals a very large number. It is estimated that as many as 1 in 300 women may carry inherited mutations of breast cancer susceptibility genes, and approximately the same proportion of Americans carry mutations that make them susceptible to colon cancer.

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What is the relationship between genes and cancer?

Cancer is a disease of genes gone awry. Genes that control the orderly replication of cells become damaged, allowing the cell to reproduce without restraint and eventually to spread into neighboring tissues and set up growths throughout the body.

All cancer is genetic, in that it is triggered by altered genes. However, just a small portion of cancer is inherited: a mutation carried in reproductive cells, passed on from one generation to the next, and present in cells throughout the body. Most cancers come from random mutations that develop in body cells during one's lifetime - either as a mistake when cells are going through cell division or in response to injuries from environmental agents such as radiation or chemicals.

Cancer usually arises in a single cell. The cell's progress from normal to malignant to metastatic appears to follow a series of distinct steps, each one controlled by a different gene or set of genes. Several types of genes have been implicated. Oncogenes normally encourage cell growth; when mutated or over expressed, they can flood cells with signals to keep on dividing. Tumor-suppressor genes normally restrain cell growth; when missing or inactivated by a mutation, they allow cells to grow and divide uncontrollably. (The inherited genes that predispose for breast and ovarian cancer, Li-Fraumeni syndrome, retinoblastoma, Wilms' tumor, and familial adenomatous polyposis are malfunctioning tumor-suppressor genes.) DNA repair genes appear to trigger cancer - and perhaps other inherited disorders - not by spurring cell growth but by failing to correct mistakes that occur as DNA copies itself, letting mutations accumulate at thousands of sites. (Genes that have been linked to hereditary colon cancer are such "proofreader" genes.)

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What does a predictive gene test tell you?

An accurate gene test will tell you if you do or do not have a disease-related gene mutation. If you do, a variety of factors can influence the gene's penetrance and the chances that you will actually develop disease. Nearly everyone with the familial adenomatous polyposis genes will - unless he or she takes

effective preventive measures - someday develop colon cancer. On the other hand, women who carry the BRCA1 breast cancer susceptibility gene have an 80-percent chance of developing breast cancer by the age of 65; their risk is high but not absolute.

Of course, even family members who escape the inherited susceptibility gene are not exempt from risk. Like anyone else, they could develop mutations in that same gene during their lifetimes. Or, they could have inherited a different, unknown susceptibility gene.

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How do scientists develop predictive gene tests?

Scientists looking for a disease gene typically have begun by studying DNA samples from members of "disease families," in which numerous relatives, over several generations, have developed the same illness such as colon cancer. Researchers look for genetic markers - easily identifiable segments of DNA - that are consistently inherited by persons with the disease but are not found in relatives who are disease-free. Then, they painstakingly narrow down the target DNA area, pull out candidate genes, and look for specific mutations.

Before a specific gene is located, linked genetic markers can be used to test members of the family under study. However, to test wider populations, it is necessary to find the gene itself. Because the DNA highway is so vast, this can be enormously difficult. In the case of Huntington's disease, it took 10 years to advance from linkage markers to the gene.

Once a disease gene has been cloned (copied to get enough to study in detail) and identified, scientists can construct DNA probes - lengths of single-stranded DNA that match parts of the known gene. (This is possible because, in double-stranded DNA, adenine in one strand always pairs with thymine in the other, and guanine pairs with cytosine.) The single-stranded probe then seeks and binds to complementary bases in the gene. When the probe has been tagged with a radioactive atom, the area of DNA it binds to - the gene - lights up. The fact that some diseases exhibit multiple mutations within the same gene adds to the complexity of gene testing.

Functional gene tests, which detect protein rather than DNA, can demonstrate not only that a mutated gene is present but also that it is actively making an abnormal protein or no protein at all.

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What is the current status of predictive gene testing for cancer?

Tests for a few rare cancers are already in clinical use. Predictive gene tests for more common types of cancer are still primarily a research tool, difficult to execute and available only through research programs to small numbers of people who have a strong family history of disease. But the field of gene testing is evolving rapidly, with new genes being discovered almost daily and innovations in testing arriving almost as quickly. For example:

· Predictive tests already are being used routinely in selected families with retinoblastoma and Wilms' tumor.

· A gene test is available for persons in the rare cancer-prone Li-Fraumeni families. However, it is available only to participants in a research study, and experts caution that it must be offered with great care, weighing benefits against risks.

· A test is in place for the gene that triggers familial adenomatous polyposis, a tendency to form hundreds of colon polyps, some of which, if not removed, will go on to become cancerous. (But the condition can also be diagnosed without the gene test.)

· A set of genes that predispose a person to a much more common type of colon cancer (hereditary nonpolyposis colon cancer, or HNPCC) has been identified in high-risk families. These genetic alterations are thought to be carried by as many as 1 million Americans, and to cause about 90 percent of all inherited colon cancers, or about 15 percent of the 160,000 colon cancers diagnosed in the United States each year. The genes have also been linked to cancers of the uterus, stomach, ovary, small intestine, gall bladder, kidney, and ureter. Very high-risk families (three or more affected members, at least one before age 50, over two or more generations) are being tested at a few research centers. A blood test is expected in a year or two.

· The BRCA1 gene mutation predisposes a person to hereditary breast cancer and ovarian cancer. A mutant BRCA1 gene on chromosome 17 is probably responsible for about 5 percent of the 182,000 cases of breast cancer predicted for a single year, and as many as a quarter of the cases occurring in women ages 45 and younger. A mutant BRCA1 gene is found in nearly half of the families with a high incidence of breast cancer and in at least 80 percent of the families with a history of both early onset breast and ovarian cancer. With the isolation of the gene, a blood test is expected, but before it becomes available, research studies must address important questions about optimum management of BRCA1 mutation carriers. (On chromosome 13, scientists have also found evidence of a second breast cancer gene called BRCA2.)

· Genes have been reported for melanoma, leukemia, thyroid and renal cell cancer, and scientists are closing in on genes for several other cancers.

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What are the benefits of gene testing?

Persons in high-risk families live with troubling uncertainties about their own future as well as that of their children. A negative test - especially one that is strongly predictive - can create a tremendous sense of relief.

A negative test, especially one that is strongly predictive, also may eliminate the need for frequent checkups and tests such as annual colonoscopy (a procedure that allows a physician to view the upper reaches of the large intestine), which are routine for high-risk families concerned about cancer.

A positive test can also produce benefits. It can relieve uncertainty, and it can allow a person to make informed decisions about his or her future.

Under the best of circumstances, a positive test creates an excellent opportunity for counseling and interventions to reduce risk. The prime example is colon cancer. When tumors are caught early, chances for survival are greatest, and screening potentially could prevent thousands of cancer deaths a year. A positive gene test sounds the alert to keep up regular screening practices (annual colonoscopies to check for precancerous polyps or the earliest signs of cancer) and to maintain healthful lifestyle measures such as a high-fiber, low-fat diet and regular exercise. Another option is surgery to remove the colon before cancer has a chance to develop.

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What additional benefits may be expected from gene testing?

Tracking down the gene that causes an inherited cancer has implications for all cancers, inherited or not. A healthy allele of the same gene, if it undergoes mutations triggered by the environment during a person's lifetime, may lead to noninherited cancers. Thus, by identifying a cancer gene, scientists are able to explore mechanisms relevant to all people with cancer.

Genes and gene markers may also provide tools for improving cancer diagnosis and treatment. By spotting a mutated gene (or its protein product) in cells shed into stool, urine, or saliva, or in tissue biopsies, doctors may be able to detect cancers years earlier than with conventional diagnostic techniques. (It has even been suggested that some day probes for a mutated gene could be injected, then traced on an x-ray.)

Evaluating cancer-preventing drugs, too, should prove more efficient once the drugs can be tested in populations that are highly likely to develop the cancer. Or, if a gene is found to produce some antitumor protein, it might be possible to synthesize that protein and use it as a drug. Ultimately, it may become possible to thwart disease with gene therapy - inactivating the flawed gene or replacing it.

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What are the limitations of gene testing?

First, current gene tests cannot provide a satisfactory answer for everyone who seems to be at risk for inherited breast or colon cancer. In some families, multiple cases may reflect shared environmental exposures rather than inherited susceptibility. Even when an inherited gene is to blame, it is not necessarily the test gene; the BRCA1 gene mutation, for example, is found in only about half of the families with hereditary breast cancer.

Second, despite major advances in DNA technology, identifying mutations remains a great challenge. Many of the genes of greatest interest to researchers are enormous, containing many thousands of bases. Mutations can occur anywhere, and searching through long stretches of DNA is difficult.

In addition, a single gene can have numerous mutations, not all of them equally influential. The cystic fibrosis gene, for instance, can display any one of more than 300 different mutations, which cause

varying degrees of disease; some seem to cause no symptoms at all. Thus, a positive test does not guarantee that disease is imminent, while a negative test - since it evaluates only the more common mutations - cannot completely rule it out.

Furthermore, predictive tests deal in probabilities, not certainties. One person with a given gene, even one that is dominant like the hereditary breast cancer gene, may develop disease, while another person remains healthy, and no one yet knows why. A gene may respond to the commands of other genes or be switched on by an environmental factor such as sunlight.

Perhaps the most important limitation of gene testing is that test information often is not matched by state-of-the-art diagnostics and therapies. Many diseases and many types of cancer still lack optimal screening procedures; it is often not possible to detect an early cancer even in an individual with a known predisposition.

In inherited breast cancer, frequent screening with mammography offers the best chance of early detection, but falls short of prevention. Moreover, mammography is least effective in the glandular breasts of young women, the very ones at greatest risk from an inherited susceptibility. For the moment, the best assurance of prevention may lie in drastic and costly surgery to remove the breasts - but even a total mastectomy can leave some breast cells behind. As for the ovarian cancer that threatens high-risk families, available screening measures often cannot discover disease in time. Here, too, women in high-risk families often opt for prophylactic surgery to remove the ovaries. To date, however, neither type of prophylactic surgery has been proven to prevent completely the occurrence of cancer.

Scientists are actively studying interventions aimed at the prevention of cancer. For example, ongoing clinical trials are evaluating the use of tamoxifen, an anticancer drug, as a breast cancer preventive. However, such approaches are still in the realm of research.

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What are the risks of gene testing?

The physical risks of the gene test itself - usually no more than giving a blood sample - are minimal. Any potential risks have more to do with the way the results of the test might change a person's life.

Psychological impact. First, there are the emotions aroused by learning that one is - or is not - likely to develop a serious disease. Many people in disease families have already seen close relatives fall victim to the disorder. The news that they do indeed carry the disease gene can elicit depression, even despair.

Few studies to date have looked directly at the outcome of gene testing for cancer. One study found that, after 3 to 6 weeks, the women identified as gene carriers experienced persistent worries, depression, confusion, and sleep disturbance. Even half of the noncarriers reported that they continued to worry about their risk status.

Family relations. Unlike other medical tests, gene tests reveal information not only about ourselves but about our relatives, and the decision to have a gene test, as well as the test results, can reverberate throughout the family. If a baby tests positive for sickle-cell trait, for example, it follows that one of his or her parents is a carrier. It is also possible for gene tests to inadvertently disclose family secrets involving paternity or adoption.

Emotions elicited by test results can produce a shift in family dynamics. Someone identified as carrying the gene may feel anger, while one who has escaped may be overwhelmed by guilt for avoiding a disease that afflicts a close relative.

Family issues are especially prominent in research programs where genetic linkage tests depend on testing many members of the same family. Some family members may not want to participate in the study or know their genetic risks. People considering gene tests may want to find out how their relatives would feel about knowing whether or not they have a disease gene or allowing the information to be given to others.

Someone who elects to have a gene test needs to consider whether or not to share the test results with other members of the family. Do they want to know? Who should be told - spouse, children, parents, fiancé? Should someone in a high-risk family be tested before she or he marries? What will a positive test mean to one's relationships? If one chooses not to learn the results of the family's gene testing, can such a request be respected? How?

Medical choices. Someone who tests positive for a cancer susceptibility gene may opt for preventive or therapeutic measures that have serious long-term implications and are potentially dangerous or of unproven value. In the first family to be tested for a BRCA1 mutation, for instance, some women chose surgery to remove their breasts - and ovaries, too, after childbearing was completed. Other families told the genetic counselor that they were not interested in even discussing surgery.

Privacy. Our genes hold an encyclopedia of information about us and, indirectly, about our relatives. Who should be privy to that information? Will a predisposition for cancer, for instance, remain secret - or could the information slip out? The concern is that test results might someday be used against a person. Some people have been denied health insurance, some have lost jobs or promotions, and some have been turned down for adoptions because of their gene status.

Small research studies have conscientiously established safeguards to keep DNA results under wraps. Assurances of confidentiality may be more difficult to come by when larger numbers of people have access to the results. Clinical test results are normally included in a person's medical records. Even if gene testing information could be kept out of the medical record, a person's need for more frequent medical checkups, for example, could provide a tip-off to susceptibility. Might a genetic flaw constitute a "preexisting condition" that would be excluded from insurance coverage?

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What is the role of genetic counseling?

In the sophisticated programs that are pioneering predictive genetic tests for cancer, genetic counseling plays a vital role. Persons considering genetic testing meet with specially trained health professionals before testing begins, when they receive the test results, and in the weeks and months afterwards.

Before testing, the counselors try to make sure that the person is psychologically prepared to cope with the possibility of a positive test, and that he or she has enough balanced information to be able to formulate a truly informed consent. If the person decides to proceed with testing, counselors help the individual and the family adjust to the test results, and they help them arrange whatever prevention and

screening measures are appropriate.

Genetic counselors are trained to help persons as they consider testing, when they receive the results, and in the weeks and months afterward.

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Who are candidates for gene testing?

Predictive gene tests for cancer are designed to identify persons who have inherited a gene mutation that may result in cancer. First candidates are families who have participated in linkage analysis studies, where the tests have been specifically tailored to pick out the gene, or gene markers, in their DNA.

Once a gene has been isolated and a test developed, testing becomes feasible in broader populations. The first candidates might be members of other very high-risk families that have had several affected members over at least two generations. Next might be persons with a family history that is less marked - perhaps one or two relatives with the disease.

Soon genetic tests for some types of inherited colon and breast cancer may be offered to the public. The targets of the tests would remain the same: individuals whose body cells carry the disease-causing mutation. These would be people who have inherited the mutant gene, including those whose family history is not apparent (for example, a woman who has acquired the breast cancer susceptibility gene through her father's side of the family). It would also include people in whom the gene mutated very early in embryonic development.

It is important to remember that predictive gene tests will be able to identify only a small proportion of the people who will get, for example, breast or colon cancer. Most cancers are not inherited, and most people who get cancer, whether or not they have relatives with it, do not have an inherited mutation.

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What obstacles stand in the way of wide-scale testing?

Having a blood test that accurately identifies a disease-causing mutation is just the first step toward wide-scale testing. Before predictive gene tests become generally available, specialists and society at large can come to grips with major technical, ethical, and economic concerns. These issues need to be addressed in carefully conducted research programs, and the answers are likely to be several years in coming.

Scientists are working to develop tests that are simple, cost-effective, and accurate. Tests need to be validated in broader populations, establishing that cancer susceptibility is caused by the gene mutation itself, not by other genetic or environmental factors shared by high-risk families. By comparing the cancer-causing genes of more and more people, researchers will be able to zero in on which of a gene's many mutations are significant and thus arrive at reasonably accurate predictions of disease risk.

The logistics of delivering a test to the thousands or millions of people who might want it - even limiting it initially to those with a strong family history - is daunting. Demand could quickly overwhelm the current extremely limited facilities and personnel available for DNA testing. Laboratories need to develop proficiency in these new techniques, and to assure accuracy and quality control.

Genetic counselors are also in short supply. People contemplating gene testing need information and guidance in order to make informed choices and weather the psychological stresses. The demand created by widespread testing would readily swamp the nation's approximately 1,200 genetic counselors, and it is likely that the task of education and counseling will fall to primary care physicians and nurses. Few primary health care providers, however, have training in this area.

Public health costs are significant. In addition to the charges for the tests themselves, there are the expenses of counseling and of follow-up clinical screening and frequent monitoring. And prophylactic surgery costs many thousands of dollars.

Finally, gene testing raises serious ethical issues, including confidentiality and discrimination. NIH is sponsoring studies of ethical issues generated by the genetics revolution, with the goal of supporting regulations and legislation to protect people from discrimination. Some states have passed legislation on health insurance discrimination and privacy. And research is under way to develop protocols to make sure that gene tests are never given without prior informed consent.

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How can someone decide whether to have a gene test?

In 1994, a Time/CNN poll asked people whether they would take a genetic test that could tell them what diseases they were likely to suffer later in life. Nearly as many people said they would prefer to remain ignorant (49 percent) as said they would like to know (50 percent).

The decision to undergo testing is a very personal one. It should also be voluntary. A person should agree to the test only if he or she desires the information. No one considering a gene test should be pressured into it by relatives, health care providers, or anyone else.

Without being told whether or not treatment or preventive measures would be available, persons were asked if they would take a test to predict diseases that would occur later in their lives. Almost the same number of people said "no" as said "yes".

In addition, unless test results can lead to direct medical benefits, experts advise parents to avoid making this choice for their children. For most adult-onset conditions, knowing a child's genetic status will not affect the course of the disease or its treatment. The decision to have a gene test should be left to the individual, at a time when he or she is mature enough to weigh the options and handle the results.

Because the issues are so complex and so new, and the consequences so profound, the decision to have a genetic test deserves careful preparation and thought. One pivotal consideration concerns whether or not any action might be prompted by the test. If the test is positive, are there opportunities for prevention or early detection?

The decision is especially wrenching for persons confronted with a disease that can be neither prevented nor cured. In one such situation, Huntington's disease, many families initially expressed interest in being tested; however, when the test actually became available, just a tiny fraction chose to go ahead with it.

The story may be different for breast and colon cancer, where there are opportunities for prevention, early detection, and treatment. Indeed, early experience from a breast cancer gene research program indicated that most of the people who had donated samples for DNA testing chose to learn the results.

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What are today's options?

We already know a lot about cancer prevention and early detection, and we don't need to wait for a gene test to put this information to good use. Regular checkups by the doctor - including mammography, prostate exams, skin exams, or Pap tests as appropriate - coupled with a healthy lifestyle are important for everyone. So is avoiding known causes of cancer: cigarette smoke, too much sunlight, unnecessary radiation. Persons who have a family history of cancer should be especially conscientious about observing these precautions, and they should make sure their doctor is aware of their family history. People with a very strong family history - a number of close relatives who have had cancer, especially if it occurred at a young age and in more than one generation - may want to schedule more frequent checkups and begin them in their twenties or thirties. Prophylactic surgery is an option, although persons considering it should realize that it brings no guarantee that cancer won't occur. Another option is to contact one of the research programs now getting under way.

It isn't necessary, though, for gene tests to arrive on the scene to give serious thought to the idea. If a gene test were available, would you want to have it? Would you want your family to be tested? What actions would you be prepared to take? And what should society be doing about the issues of privacy and discrimination? The present moment, when genes are being discovered but before tests become widely available, offers a small window of opportunity to prepare for the future.

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