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Genetics in the Courtroom: An Introduction

This issue of The Judges' Journal is dedicated to a future rapidly taking form, a future in which controversies of every sort will be debated in terms of diseases, disease carriers, predispositions, and susceptibilities. Genetic tests, scientists predict, will be customized to detect thousands of these characteristics and states at the molecular level. This issue of The Judges' Journal thus serves as an invitation to consider that future, to get ready for challenges in the courtroom that could prove both disturbing and exhilarating. Unanswered legal and social questions will abound, some of which can be articulated today. For example, who owns genetic information? Are genetic proofs of diminished moral capacity admissible in capital crimes trials -- at both the liability and the penalty phase proceedings? What will happen to concepts of free will and responsibility in an era of genetic causation?

In the near future, genetic tests will be offered in evidence in virtually any courtroom. In criminal cases, genetic identification is now a commonplace technology. Genetic proofs routinely are offered in paternity actions, and genetic tests will soon flood the courtroom with evidence purporting to support medical and nonmedical cases alike. All have ethical and social implications. Is a predisposition for colon cancer, for example, a legally justified reason to bar a person from mortgage insurance? Should predictive diagnostic information derived from genetic tests be suppressed in the absence of measures to prevent or cure? Will genetic causation be overdetermined in both concept and evidence?

In turning judicial attention to some of these ripening issues, we are spurred by the velocity of genetic research and the vigorous activity to turn it into commercial products. Genetic tests are big business and are largely unregulated. Genetic counseling is an irregular calling just taking form as a profession. A 1996 New Jersey case, Safer v. Estate of Peck, 291 N.J. Super. 619, 677 A.2d 1188, questions the availability of a cause of action based on genetically transmittable disease. Is there a duty to warn, the case asks, when a physician detects a genetically transmitted disease such as colon cancer? Conflicts of law surface immediately. What happens to the established privileges governing the patient-physician relationship? New conflicts come into view. Will the availability of gene therapy provide early in the new millennium many new cases of first impression that integrate scientific, clinical, legal, and ethical perspectives?

These concerns flow from an extraordinary promise -- the Human Genome Project's 2005 objective to map and sequence every one of a human being’s estimated seventy thousand genes. Hardly a day goes by without notification of a new gene discovery in the popular press. Sometimes these discoveries are valid and durable. The discovery of a gene family that suppresses tumor growth, for example, may presage new cancer therapies. Other discoveries remain to be replicated. A gene associated with "anxiety," for example, was announced a year ago and failed of replication.
Pressure for gene therapy mounts as biological technologies promise means for altering our genes and those of unborn generations. The social and ethical issues that are being raised transcend those of the law.

Supported by a grant from the Human Genome Project at the U.S. Department of Energy, the Einstein Institute for Science, Health and the Courts (EINSHAC) has initiated a series of conferences for judges on cases involving genetics, molecular biology, and biotechnology. The first conference was held mid-May 1997, cohosted by the Superior Court of the District of Columbia and the U.S. District Court for the District of Columbia. Fifteen jurisdictions sent representatives. Cases involving scientific evidence of natural inheritance will be considered in the series against a scientific backdrop of genetics, molecular biology, and biotechnology. Future conferences will be held in Chicago, Salt Lake City, Orlando and Cape Cod throughout 1998.

This theme issue of The Judges' Journal discusses some developments and controversies that are being explored in these conferences. The first section highlights the scientific backdrop. The second addresses some issues associated with the adjudication of criminal and civil cases in which molecular genetic evidence is introduced. Together, these articles comprise a primer. A separate handbook and video summaries prepared in relation to the conference series will be available from EINSHAC later this year. Taken together, all of these materials begin an effort to archive resources that judges may well find useful when genetics-related cases are assigned.

We are deeply grateful to Fred Melcher, Editor of The Judges Journal, and to the American Bar Association Judicial Division's leadership for the opportunity to present this issue on genetics in the courtroom. Our thanks also go to John Fallahay, the Issue Editor, for his editorial expertise, project management, and helpfulness in preparing the volume. We wish to note as well our appreciation to the Department of Energy Human Genome Project for technical and grant assistance in the production of this theme issue.

All that remains is to encourage readers to absorb the issues that will soon confront them in the courtrooms of this nation.

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Introducing the Human Genome Project: Its Relevance, Triumphs, and Challenges

by Ari Patrinos and Daniel W. Drell

an article that originally appeared in a special genetics issue of The Judges' Journal of the American Bar Association
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Odds are that you have heard of the Human Genome Project. You have probably seen it mentioned on page 8 of the *New York Times* or the *Wichita Eagle*. Perhaps it was alluded to in the recent spate of magazine articles or television discussions on cloning. But even if you have read news stories or heard tangential references thereto, the odds are also that you do not really know what the Human Genome project is, how it came to be, or what it will mean to you, your family, or your life.

If you are a judge or lawyer, you will need to know about the Human Genome Project because its scope is pervasive and its potential legal implications are vast. Information gleaned from the project is sure to be playing in a courtroom near you in the not-too-distant future. You have probably already seen cases involving forensic DNA evidence in paternity suits or criminal prosecutions. If so, you have merely witnessed the tip of the iceberg. Discrimination cases based on the dissemination of genetic testing information to official or private entities will be featured shortly. Motions for injunctive relief will be filed based on irreparable harm to general health, life, or the species posed by gene therapy and other biotechnology regimes. There will be judicial review of the administrative regulation of genetic testing methods and genetic counseling services. Soon we can even expect criminal jurisprudence of claims challenging the validity of individual responsibility based on free will considerations in light of the discovery of genetic traits that, it will be claimed, predispose certain individuals to violence or antisocial, thrill-seeking behavior.

Experts will present complex evidence for one party, and they will be met by experts from the other. Your limited awareness of the scientific "knowledge" gathered in the last two decades will probably handicap you. If so, you will be like many of your peers and community members. However, unlike many, you will not be able to throw up your arms, admit ignorance, and choose to walk away. It will be your job to present this type of evidence clearly, or to determine whether it should be allowed in the courtroom, or to make sure that jurors who are completely unversed in its implications are made as familiar as possible with genetic technology so that they can understand the cases before them and rule fairly and adequately.

To do so, you will need a working familiarity with the Human Genome Project and the issues of genetics as they will present themselves in the courtrooms of America.

**SOME NECESSARY BACKGROUND**

Long before there was a formal Human Genome Project (HGP), the Department of Energy (DOE) and its predecessor agencies had been interested in developing sensitive methods to detect changes to genetic materials induced by ionizing radiation and to understand the related health effects.[1] It has been known for some time that the genetic-information-containing DNA is the part of a cell that is the most sensitive to the effects of radiation and other pollutants, even in low doses.[2] As new technologies for understanding and working with DNA were developed in the 1980s, the idea arose to sequence the entire human genome systematically, and with this idea arose the HGP. It was recognized early on that once this project was completed, it would furnish a comprehensive reference source that others could build on without having to repeat the research from scratch.

**Understanding the Basic Science.** Perhaps we are outstripping ourselves. You are probably asking, Exactly what is the HGP? Simply put, the HGP is an attempt to map completely the entire spectrum of genetic materials that can be found in all human beings. It is a research effort initiated by the DOE and jointly managed by the DOE and the National Institutes of Health (NIH). A unifying fact of human genetics is that all humans have genomes --the complete set of our genetic instructions on the 23 pairs of chromosomes within each of us --that are 99.9 percent identical in sequence. The DNA molecules that carry these genetic instructions are linear, information-containing molecules made up of four simple bases or building blocks --adenine, cytosine, guanine and thymine --that pair up to form the well-known DNA double helix. Although each one of our cells contains about six billion base pairs of DNA, three billion from each parent, we think that our differences are determined by only about one base pair in each thousand. Thus, at this most fundamental level of molecular definition, what we share dwarfs what distinguishes us.

The HGP will determine the complete sequence of the DNA from a typical human cell and will provide information and resources to understand some of the critical differences that make us individuals and that often contribute to diseases. Such information and resources, and the resulting insights garnered therefrom, will contribute to many areas of biology and biotechnology beyond those that are strictly health related, but they will also open the way to new...
approaches to treating diseases.[3-5] The discovery in 1994 of two genes involved in the origins of breast cancer exemplified the promise of genomic research.[6, 7] This discovery was made by a large group of researchers with critical help from resources generated by the DOE.

The DOE's Participation. Given the magnitude of the task of mapping and sequencing the human genome, there was an early appreciation that the unique capabilities and resources of the DOE National Laboratories would be critically important. These labs could contribute specialized resources, such as sophisticated engineering and high-performance computing, and could facilitate the close collaboration of various scientists from many fields, including molecular biologists, engineers, physicists, chemists, and mathematicians. Other unique assets of the DOE labs were the synchrotron light sources and neutron sources that have facilitated the relatively new science of structural biology. Structural biology, together with computational biology, helps to define the three-dimensional structures of biomolecules and to complement the work on genomics and gene function in general.

With the Office of Management and Budget's approval, the DOE committed its first funds for human genome research in October 1986. After the NIH started its own genome effort the next year, a coordinated project was formally launched. In 1988, the DOE and the NIH signed a Memorandum of Understanding that committed the two agencies to work together by coordinating activities and leveraging their respective strengths as assets.[8] The official "clock" on the project was started on October 1, 1990. At the same time, a joint five-year plan for the project was agreed to, with the delineation of specific technical milestones in mapping and sequencing. Because of rapid progress in several technical areas, especially genome mapping, the joint plan was revised four years ago with the publication of a new and more ambitious five-year plan.[9]

Economic and Societal Implications. One goal of the HGP is to localize all of the estimated 80,000 genes on the human chromosomes and to determine the sequence of all three billion units of DNA that constitute one set of those chromosomes. This information will vastly accelerate studies that will characterize what those genes do and how disease can result from errors in their functioning. An important element of the HGP is to enable technologies that will allow biologists to uncover gene function more efficiently. This is important because while the HGP will describe the human genome in molecular detail, its longer term and more profound impact will be to reveal critical mechanisms of human biology and supply the medical context within which investigations on the molecular pathology of human diseases can most efficiently take place. This will lead to a future medicine in which prevention will be firmly rooted in mechanistic knowledge and potential interventions can be more targeted and effective.[10] We also believe that this will lead to more cost-effective medical care since prevention is almost always cheaper than treatment.

The promise of the HGP goes far beyond medicine to many other areas of science. In addition to its many implications for medicine and human health --which includes mutation detection, more accurate risk assessment, more precise disease diagnosis, more rapid characterization of genetic damage and repair processes, and the identification of precision pharmaceuticals based on intimate biological knowledge --this international project is creating technologies and resources that will be applied to the characterization of the genomes of other living organisms. This information will, in turn, provide us with important new practical applications in energy, environmental protection, agriculture, and industrial processes. The appeal of this targeted approach to biology can be seen in the recent establishment of genome projects for several microbes,[11] agricultural crops,[12] and animals.[13] We are already experiencing a dramatic technological revolution affecting many of America's most important enterprises, such as agriculture, chemicals, medicine, and energy production, leading to environmentally sustainable technologies. For example, new varieties of plants will be developed for renewable biomass-based energy production. Biological catalysts such as enzymes or catalytic antibodies will be designed to order for mining and processing, just as one designs the mechanical components of industrial systems. Bioprocessing will minimize pollution, while bioremediation will clean up wastes. The genetic information encoded in the genomes of many organisms will lead to designer drugs that will revolutionize medicine and create new materials for specific applications. We can reasonable expect that the biotechnology of the near future will accomplish society's objective of sustainable development.

Tremendous insights are emerging from genome studies in model systems, because fundamentally a cell is a cell is a cell. Over eons, evolution has conserved the biochemistry that worked well for the simplest organisms and has adapted this biochemistry to respond to changing environmental conditions. The genes that determine structure and function for similar single cell organisms are often similar, in sequence and products, to those that determine the structure and
function of human cells.[14] By studying simple cells and simple organisms, we will better understand comparable
structures and functions in human cells. For example, the work on comparative genomics at the Oak Ridge National
Laboratory and elsewhere exploits the similarities of mouse and human genomes.[15-18]

THE ACHIEVEMENTS AND CHALLENGES OF THE HGP

Specific Medical Advances. Without meaning to be overly "scientific," we would like to highlight some recent
achievements of the genome program. Understanding these achievements will allow greater appreciation of just what
the project is and what its cumulative effect may be. In 1995, for example, the highest resolution physical maps for
human chromosomes were completed by the Los Alamos National Laboratory and the Lawrence Livermore National
Laboratory for chromosomes 16 and 19, respectively.[19, 20] The chromosome 19 map has already contributed to the
characterization of the genetic defect underlying the disease of myotonic dystrophy and to the description of the
unusual genetic mechanism of aberrant triplet repeats that is now known to contribute to the onset of at least nine
diseases, including Huntington's disease.[21-24] Genes mapped to chromosome 16 include those involved in Batten's
disease, polycystic kidney disease, Crohn's disease, forms of breast and prostate cancer, and Fanconi's anemia, as well
as many others.[19] In addition, the DNA repair genes HHR23A, XRCC1, and ERCC2, as well as genes involved in
olfactory receptors, Alzheimer's disease, and one form of migraine headache, have been discovered on chromosome
19.[20]

In a different context, but highly important, the Lawrence Berkeley National Laboratory has produced two megabases
of human sequence, using directed sequencing, just in the last year or so. Lee Hood at the University of Washington in
Seattle has sequenced nearly 700,000 consecutive base pairs of DNA from the human T cell receptor complex, as well
as a comparable amount of mouse T cell receptor DNA.[25] These sequences have provided surprising insights into the
evolution and function of certain white blood cells important for many immune responses to invading pathogens and
are widely thought to be involved in both autoimmune diseases and protection against early tumor development.

Additional accomplishments include advances in technologies that are speeding up DNA sequencing, among them the
development of novel "vectors" (critical for the manipulation of DNA in fragment sizes that can readily be
characterized and studied), particularly Bacterial Artificial Chromosomes or BACs.[26] A DOE-funded BAC library
contributed to the discovery of the Breast Cancer-1 gene by supplying the particular BAC containing the appropriate
DNA fragment from chromosome 17.[6] Another library from a DOE-supported researcher at Roswell Park Memorial
Institute was important for the identification of the BRCA2 gene on chromosome 13.[7]

The Importance of Gene Databases. A major challenge for the entire HGP, and one that the DOE continually
emphasizes, is the development of informatics tools -- e.g., data management and analysis -- to deal with the expected
avalanche of HGP data. Both the DOE and the NIH firmly plan to make all the HGP data available to the public in the
shortest possible time after its acquisition and verification. Furthermore, the access to the HGP data must be extremely
user-friendly, so that all biologists -- indeed, all scientists -- can use the data in their research. The Genome Data Base
(GDB) is one of the important databases supported by both the NIH and the DOE and is the worldwide repository for
genome mapping data[27] that may be the model for future databases of the HGP. While the main GDB central facility
is in Baltimore, an increasing number of interconnected "nodes" have been established at various international
locations to facilitate access via the Internet by researchers around the world. This is part of the "federated information
infrastructure" concept[28, 29] that allows users to link their computers to a global network of different related
databases distributed around the world. Another example of a DOE-supported HGP database is the Genome Sequence
Data Base (GSDB) based at the National Center for Genome Resources (NCGR) in Santa Fe.[30] The GSDB collects
primarily genome sequence data and is connected with the GDB through the federated infrastructure. Our ambition is
that these and other databases will work together to provide access to, and answers about, the human genome.

Why will these databases be so important in the future? Consider that three billion letters, if printed, would fill some
200 major city phone books, a cumbersome way to store data. Locating the few thousand letters of interest would
require a major effort. Computers will play a critical role in enabling physicians, researchers, or anyone else to access
and use the results of the HGP. In addition, we estimate that only about 5 percent of the genome sequence is actually
used for the determination of expressed proteins, and that small portion is scattered across the genome. The sequence
for any given gene may exist as a number of noncontiguous pieces that are only properly assembled at the time of
transcription into messenger RNA immediately prior to translation into protein.[31] (Messenger RNA is the "working copy" of the genetic information contained in the DNA "master copy" stored in the chromosome.) A little understood mechanism called alternative splicing allows the same piece of DNA to generate different protein products under different circumstances, making the understanding of gene organization more complex from the standpoint of understanding the roles of genes in disease processes.[31]

From the beginning, the DOE genome program has been a highly focused but constantly evolving program. Over the next several years, a much larger emphasis will be placed on high-throughput sequencing, determining millions of base pairs annually. The principal goal of the HGP remains the complete sequence of a generic human genome by 2005, and we expect to fulfill this goal. Our optimism stems from recent successes in sequencing the genomes of simpler organisms, coupled with improvements in sequencing reagents and instrumentation, as well as the development of more effective clone resources. The NIH has started six pilot projects for high-throughput sequencing, and the DOE is also committing an increased portion of its HGP budget to high-throughput DNA sequencing. Ultimately, the sequencing will be done by many laboratories and universities around the globe. Even as this effort begins, the DOE and the NIH, among others, are exploring how we need to prepare ourselves, both as scientists and science managers, for the challenges of the "next generation" of biology that will follow.

CONFRONTING THE ETHICAL, LEGAL AND SOCIAL ISSUES

James Watson, who won the Nobel Prize in Physiology in Medicine in 1962 for codiscovering the structure of DNA, made a seminal contribution to the HGP when he recognized that knowledge derived from genome studies has broader medical and societal implications. This led directly to the establishment of a program devoted to the ethical, legal, and social implications (ELSI) of genome research. One goal of the ELSI program is to address the implications of vastly increased genetic information and protocols on individuals and society. Another ELSI goal is to identify and develop appropriate policy options to confront and contain future ELSI problems. Because we know that "genetic information" has been misused previously in the United States and other countries, we must ensure that such mistakes are never repeated. Both the DOE and the NIH are optimistic that the ELSI program can contribute to the integration of HGP results in ways that are less disruptive, painful, or destructive than those in the past.

The list of ELSI issues is long and virtually all of them have legal ramifications. They include the fair use of genetic information; the impact on genetic counseling and medical practice; the effects on personal reproductive decisions; past uses and misuses of genetic information; privacy implications of personal genetic information in various settings, e.g., the work place, schools, or in the context of adoptions; issues of the commercialization and intellectual property protection of genome results, including DNA sequences; conceptual and philosophical implications; implications of personal genetic variation; and genetic literacy and the understanding of genetic information, particularly information related to complex conditions that involve multiple genes and genetic-environmental interactions. This last category, involving health issues like mental illness, heart disease, diabetes, or cancer, represents the most complex of ELSI issues because the underlying science is poorly understood.[32, 33] For example, informing a woman that she carries an allele at BRCA1 that is associated with a high lifetime risk of developing breast cancer is a serious issue, particularly if treatment options are difficult, painful, debilitating, or oftentimes less than successful. A recent study suggests that many women from high-risk families simply prefer not to know.[34] However, other individuals or entities may want to know about such conditions, including insurers and employers (who often are responsible for insure their employees). Congress has started to debate and legislate these issues. The Health Insurance Portability and Accountability Act, sponsored by Senators Kennedy (D--Massachusetts) and Kassebaum (R--Kansas), passed by the 104th Congress in 1996 and signed into law by President Clinton, offers some limited protection from loss of health insurance due to genetic information. The extent of this protection is undoubtedly an issue that courts will have to adjudicate.

However, before we get completely engrossed in the complexity and uncertainty of these issues, we should carefully note a few of the ELSI program's successes. Developed by a DOE ELSI grantee, a model genetic privacy bill was introduced into the U.S. Senate in November 1995, and parts of it have been incorporated into the Genetic Confidentiality and Non-Discrimination Act introduced by Senator Pete Domenici (R--New Mexico) in June 1996. While the 104th Congress did not act on this legislation, a revised version has been introduced into the 105th Congress. Workshops on genetics have been presented to help judges better appreciate the relevance of genetic
information in the courtroom, and publications like this special issue of The Judges' Journal have been prepared and disseminated. We have produced curricula for high schools that will affect approximately 2.5 million students of high school biology, many of whom may be studying biology and its societal implications for the last time in their lives.[35] Another DOE ELSI project is exploring the implications of patenting genome sequences on the transfer of genome information and technologies to the commercial sector, a subject of considerable controversy and one that will be hotly debated over the next several years as the products of genome research move into the marketplace.[36, 37]

Many of the ELSI issues that face us are not new to medicine, but they will become more prominent as the HGP progresses. Our challenge is to anticipate them whenever possible and to reduce their negative impact where practicable. The DOE ELSI program has maintained close contact and coordination with the ELSI program of the NIH's genome program, and the two agencies have jointly supported the DOE-NIH ELSI Working Group, which coordinates ELSI policy development between the two programs.

We see many ELSI challenges in the future. Informed consent for participants in genetic research will remain an important issue. Genetics involves shared familial information, and the diagnosis of one person has direct implications for his or her family members. It is extremely important that patients and research participants understand what information and future predictive insights about them may emerge from genetic studies, particularly when they involve genetic testing or screening for multigenic and predisposition diseases. For example, over six hundred mutations in the gene for the cystic fibrosis transmembrane regulator can lead to cystic fibrosis.[38, 39] Many experts think that only seven of these mutations are responsible for 85 percent of the cases of cystic fibrosis seen clinically, and it is these seven for which most people are tested. However, a negative test for cystic fibrosis disease-associated alleles does not necessarily mean that a person does not have a risk for cystic fibrosis. The gene for breast cancer susceptibility (BRCA1) is another case in point. Over 150 alleles in the gene have been discovered, [40] and one in particular is common in women of Ashkenazi Jewish background.[41] The BRCA1 region is very large, [7] and the number of alleles that actually predispose to breast cancer is not yet known. We also know very little about other influences that are necessary (along with one of these mutations) for breast cancer. What do you tell someone who tests positive for a disease-associated allele when you can only be vague about its clinical implications? What responsibilities do physicians and counselors have in the communication of risk information to patients when the risks themselves are poorly understood? What liability issues accompany genetic information? Can genetic information be "owned" and, if so, by whom and under what circumstances? These and other issues that arise from genetic information will challenge the courts and will be exacerbated as we get better at "reading" and interpreting the content of our genomes.

COURTS IN THE HGP CONTEXT

A major challenge in the judicial arena is to introduce the most current and rigorous scientific information related to genomics in a form that is most useful and understandable to judges and juries. Molecular genetics, like some other sciences, can be complicated and often confusing, even to those with scientific background and training. Because molecular genetics is also changing continuously, one can easily pit one scientific "expert" against another, with no clear mechanism to adjudicate between the two. Most scientists are uncomfortable with what they perceive to be the rigid demands of judicial proceedings and shy away from"beyond reasonable doubt" pronouncements. The all-too-frequent result is that the scientific perspective is represented by fringe elements of the scientific community that may distort the state of the science. Although such distortion is not unique to genetics, prominent and widely publicized examples have been witnessed during the last several years, and the future unfortunately holds the promise of many more.

The scientific community involved in genetics need to mobilize quickly to deal with this issue, and the ELSI element of the HGP could provide a useful organizing mechanism. One model for arriving at scientific consensus that could be explored is the one developed by climate scientists to advise governments on climate change from man-made emissions of greenhouse gases. Organized by the United Nations in 1988, the Intergovernmental Panel on Climate Change (IPCC) has brought together the international scientific community involved in global climate issues to assess periodically the state of the science of climate change prediction, the associated impacts, and the optimum approaches to dealing with mitigation and adaption to the predicted changes.[42] The IPCC has employed rigorous procedures of peer review and quality assurance and has accomplished the remarkable feat of arriving at consensus statements that have guided governments in their pursuit of policies that are addressing the threats of manmade climate change. It will
be an interesting challenge to explore whether the IPCC model can be adapted for the use of genetic information in the judicial arena, especially since the 1993 Supreme Court decision in Daubert v. Merrell-Dow[43] places responsibility on individual trial judges to determine the relevance--and this the admissibility-- of scientific evidence.

REFERENCES

Some Currently Available DNA-Based Gene Tests

Gene tests for the disorders listed below were available as of 1996 from clinical genetics laboratories approved by New York State. Test names and a description of the diseases or symptoms thereof

What Can the New Gene Tests Tell Us?

by Denise Casey


A cartoon appearing almost half a century ago in The New Yorker featured a young boy watching his father review his report card. "What do you think the trouble with me is, Dad?" he asks with artful innocence. "Heredity or environment?" In one timeless scene, the cartoonist conveyed our fascination with genetics and the ongoing debate over just how much we can attribute to the genes we inherit from our parents.

Lately we have learned a lot about our genetic legacy. We now know that, in fact, all diseases have a genetic component, whether inherited or resulting from the body's response to environmental stresses like viruses or toxins. The successes of the Human Genome Project (HGP) have even enabled researchers to pinpoint errors in genes--the smallest units of heredity--that cause or contribute to disease.

The ultimate goal is to use this information to develop new ways to treat, cure,
appear in parentheses. Susceptibility tests are noted by an asterisk and provide only an estimated risk for developing the disorder.

- **Alpha-1-antitrypsin deficiency** (AAT; emphysema and liver disease)
- **Amyotrophic lateral sclerosis** (ALS; Lou Gehrig's Disease; progressive motor function loss leading to paralysis and death)
- **Alzheimer's disease** (APOE; late onset variety of senile dementia)
- **Ataxia telangiectasia** (AT; progressive brain disorder resulting in loss of muscle control and cancers)
- **Gaucher disease** (GD; enlarged liver and spleen, bone degeneration)
- **Inherited breast and ovarian cancer** (BRCA 1 and 2; early onset tumors of breasts and ovaries)
- **Hereditary nonpolyposis colon cancer** (CA; early onset tumors of colon and sometimes other organs)
- **Charcot-Marie-Tooth** (CMT; loss of feeling in ends of limbs)
- **Congenital adrenal hyperplasia** (CAH; hormone deficiency; ambiguous genitalia and male pseudohermaphroditism)
- **Cystic fibrosis** (CF; disease of lung and pancreas resulting in thick mucous accumulations and chronic infections)
- **Duchenne muscular dystrophy/Becker muscular dystrophy** (DMD; severe/mild muscle wasting, deterioration, weakness)
- **Dystonia** (DYT; muscle rigidity, repetitive twisting movements)
- **Fanconi anemia, group C** (FA; anemia, leukemia, skeletal deformities)
- **Factor V-Leiden** (FVL; bleeding disorder)
- **Fragile X syndrome** (FRAX; leading cause of inherited mental retardation)
- **Hemophilia A and B** (HEMA and HEMB; bleeding disorders)
- **Huntington disease** (HD; or even prevent the thousands of diseases that afflict humankind. But the road from gene identification to effective treatments is long and fraught with challenges. In the meantime, biotechnology companies are racing ahead with commercialization by designing diagnostic tests to detect errant genes in people suspected of having particular diseases or at risk for developing them.

An increasing number of gene tests are becoming available commercially (SEE BOX: Some Currently Available DNA-Based Gene Tests), although the scientific community continues to debate the best way to deliver them to a public and medical community that are unaware of their scientific and social implications. While some of these tests have greatly improved and even saved lives, scientists remain unsure of how to interpret many of them. Also, patients taking the tests face significant risks of jeopardizing their employment and/or insurance status. And because genetic information is shared, these risks can extend beyond them to their family members as well.

Even so, many more tests are in the works as dozens of new biotechnology companies vie to spin genetic data into gold. In the United States alone over four hundred laboratory programs aim to develop gene tests for disorders ranging from arthritis to obesity, and the list grows daily. The technology continues to advance rapidly, and future versions will allow simultaneous testing for hundreds of different genetic mistakes. The volume of available personal genetic data is on the brink of exploding, increasing the urgency of addressing ethical, legal, and social implications thereof. This was not unexpected. From its start over six years ago, HGP planners have dedicated at least 3 percent of the budget to grappling with just these issues.

Beginning with a short introduction to ground the reader in the DNA science underlying gene tests, this article explains some of the tests, their limitations, and the extraordinary potential of DNA medicine for the twenty-first century.

**A GENETIC SCIENCE PRIMER**

A gene is simply a piece of DNA, the chemical responsible for storing and transferring all hereditary information in a cell. Genes accomplish this by containing recipes for making proteins, the true workhorses of all our trillions of cells. All living organisms are made up largely of proteins, which provide the structural components of all our cells and tissues as well as specialized enzymes for all essential chemical reactions. Through these proteins, our genes determine how well we process foods, detoxify poisons, and respond to infections. Although our cells have the same genes, not all genes are active in all cells. Heart cells synthesize proteins required for that organ's structure and function, liver cells make liver proteins, and so on.

In humans and other higher organisms, a DNA molecule consists of two ribbon-like strands that wrap around each other, resembling a twisted ladder. The ladder rungs are made up of chemicals called bases, abbreviated A, T, C, and G. Each rung consists of a pair of bases, either A and T or C and G. We have three billion base pairs (six billion bases) of DNA in most of our cells; this is our genome. With the exception of identical twins, the sequence of the bases--the order of As, Ts, Cs, and Gs--is different for everyone, which is what makes each of us unique. Variation in base sequence, along with environmental factors, accounts for all our diversity, including disease.

The DNA making up our genome is divided into tightly coiled packets called
usually midlife onset; progressive, lethal, degenerative neurological disease)

- **Myotonic dystrophy** (MD; progressive muscle weakness; most common form of adult muscular dystrophy)
- **Neurofibromatosis type 1** (NF1; multiple benign nervous system tumors that can be disfiguring; cancers)
- **Phenylketonuria** (PKU; progressive mental retardation due to missing enzyme; correctable by diet)
- **Adult Polycystic Kidney Disease** (APKD; kidney failure and liver disease)
- **Prader Willi/Angelman syndromes** (PW/A; decreased motor skills, cognitive impairment, early death)
- **Sickle cell disease** (SS; blood cell disorder; chronic pain and infections)
- **Spinocerebellar ataxia, type 1** (SCA1; involuntary muscle movements, reflex disorders, explosive speech)
- **Spinal muscular atrophy** (SMA; severe, usually lethal progressive muscle wasting disorder in children)
- **Thalassemias** (THAL; anemias - reduced red blood cell levels)
- **Tay-Sachs Disease** (TS; fatal neurological disease of early childhood; seizures, paralysis)

Chromosomes, which reside in the nucleus of each cell. Each chromosome is a single DNA molecule, and lengths range from 50 million to 250 million bases. Scientists can distinguish the chromosomes by size, distinctive staining patterns, and other characteristics.

Most cells have 46 chromosomes, 23 from each parent. A set of 23 contains 22 numbered chromosomes (1-22) plus either an X or Y sex-determining chromosome. Females receive an X from each parent, and males get one X and one Y. Sperm and egg cells only have 23 chromosomes, and mature red blood cells have none.

Chromosomes are not continuous strings of genes. Genes are interspersed among millions of bases of DNA that do not code for proteins (noncoding DNA) and whose functions are largely unknown. In fact, genes constitute only a tiny fraction of the human genome, a mere 3 percent. Scientists estimate that we have about 60,000 to 80,000 genes, whose sizes range from fewer than one thousand to several million bases. We have two copies of every gene, one from each of our parents.

**FROM DIVERSITY TO DISEASE**

For all our outward variation, we are surprisingly alike at the DNA level. Differences account for only one tenth of 1 percent of our DNA (about three million base pairs). Yet DNA base sequence variations are responsible for all our physical differences and influence many of our other characteristics as well. Sequence variation can occur in our genes, and the resulting different forms of the same gene are called alleles. People can have two identical or two different alleles for a particular gene. Variation also occurs outside the genes in the noncoding part of our DNA.

**Mutations.** While most DNA variation is normal, harmful sequence changes sometimes occur in our DNA that cause or contribute to disease. All DNA sequence changes--called mutations--are either passed down from parent to child (in the sperm or egg cells) or acquired during a person's lifetime. The vast majority of diseases are due to acquired changes, known as sporadic mutations. These mutations can arise spontaneously during normal functions, as when a cell divides, or in response to environmental stresses such as toxins, radiation, hormones, and perhaps even diet. Nature provides us with a system of finely tuned repair enzymes that find and fix most DNA errors. But as we age, our repair systems may become less efficient and allow us to accumulate uncorrected mutations. This can result in diseases such as cancer.

Depending on where in our genome they occur, mutations can have devastating effects or none at all. If they are small and fall in the vast sea of noncoding sequences, no one might be the wiser. Changes within genes, however, can result in faulty proteins that function at less-than-normal levels or those that are completely nonfunctional, causing disease. (For a list of some of the most commonly inherited disorders, SEE BOX: Some of the Most Common Inherited Disorders).

Sometimes only a tiny change in DNA sequence will lead to a serious disease. The substitution of just a single base, for example, leads to sickle cell anemia. Other diseases are caused by deletions or additions of single or multiple bases. Too many repetitions of a particular sequence of three DNA bases can doom a
person to Huntington's disease, a fatal neurological disorder; Fragile X syndrome, the most common form of inherited mental retardation; or myotonic dystrophy, a muscle-wasting disease. Other diseases can result from large rearrangements of DNA.

**Single-Gene and More Complex Diseases.** Some four thousand diseases are thought to be caused by a mutation in a single gene that is inherited from one or both parents. Most of these disorders are very rare, accounting for only about 3 percent of all disease. Some occur more frequently in particular ethnic groups. Among the more common inherited disorders for which single, causative genes have been identified are sickle cell anemia (African Americans and Hispanics), cystic fibrosis (Caucasians), and Tay Sachs (Ashkenazi Jews).

For most diseases the causes are much more complex. The common scourges afflicting Western civilization are thought to be due to a variety of gene mutations, perhaps acting together, or to a combination of genes and environmental factors. Heart disease, diabetes, hypertension, cancers, Alzheimer's disease (AD), schizophrenia, and manic depression are all examples of complex diseases.

Except for rare forms of these disorders that are inherited in some families, single mutated genes associated with complex diseases are not considered causative. Rather, they confer a susceptibility to their bearers and, given the right combinations of genes and environmental factors, will allow a disease to develop. Untangling the genetic and environmental contributions to complex disease will be one of the greatest challenges for medical researchers in the next century.

**Finding Disease Genes.** To find a gene that is a likely candidate for involvement in disease, scientists must search for DNA changes that are linked only with people who have a particular disease. Searching randomly through three billion base pairs of DNA for tiny changes that may be linked with disease is no easy task. Scientists labored through 10 years of tedious, painstaking work to find the genes for both Huntington's disease and cystic fibrosis. Thanks to the HGP, researchers now have some guidance from chromosome maps. Generated within the last two years, these maps specify thousands of unique DNA regions that act as mile markers along the chromosomal highways. These types of markers, which form a grid of known locations across every chromosome, are especially informative to researchers searching for small differences in DNA sequence among the members of large families. The high-quality maps have dramatically sped up the discovery of disease genes, reducing the hunt from years (at a cost of several million dollars) to months in some cases.

Luck plays an important part in any gene hunt. Researchers studying large families with several cases of an inherited disease scan the genomes of all family members for any changes in marker DNA sequence that correlate with the presence of disease. How long it takes to find a disease gene this way depends in large part on the particular markers chosen.

In fall 1996, a region on chromosome 1 was found to be associated with a form of prostate cancer that runs in families. Researchers examined over 300 DNA marker regions in the genomes of some 100 families and compared the DNA sequences of affected individuals with healthy ones. The location of the implicated region containing the mutation was made available to the entire
research community via the Internet. This region is now the focus of an intensive search for the causative gene by many groups around the world. Although the type of prostate cancer studied in these families is rare, researchers expect it will lead to insights into how the more common forms arise.

Once the disease genes themselves or their approximate chromosomal regions are finally identified, academic and commercial laboratories often translate these findings into gene tests that can detect the particular mutations associated with a disease.

**GENE TESTS**

Gene tests, also called DNA-based tests, are the newest and most sophisticated of the techniques used to test for genetic disorders, and involve direct examination of the DNA molecule itself. Other genetic tests include biochemical tests for such gene products as enzymes and other proteins, and microscopic examination of stained or fluorescent chromosomes. Genetic tests are used for several reasons, including:

- carrier screening, which involves identifying unaffected individuals who carry one copy of a gene for a disease that requires two copies for the disease to be expressed;
- prenatal diagnostic testing;
- newborn screening;
- presymptomatic testing for predicting adult-onset disorders such as Huntington's disease;
- presymptomatic testing for estimating a risk for developing adult-onset cancers and Alzheimer's disease;
- confirmational diagnosis of a symptomatic individual; and
- forensic/identity testing.

In gene tests, scientists scan a patient's DNA sample for mutated sequences. A DNA sample can be obtained from any tissue, including blood. For some types of gene tests, researchers design short pieces of DNA, called probes, whose sequences are complementary to the mutated sequences. These probes will seek their complement among the three billion base pairs of an individual's genome. If the mutated sequence is present in the patient's genome, the probe will bind to it and flag the mutation. Another type of DNA testing involves comparing the sequence of DNA bases in a patient's gene to a normal version of the gene. Cost of testing can range from hundreds to thousands of dollars, depending on the sizes of the genes and the numbers of mutations tested.

Gene testing already has dramatically improved lives. Some tests are used to clarify a diagnosis and direct a physician toward appropriate treatments, while others allow families to avoid having children with devastating diseases (SEE BOX: Cheating the Fates) or identify people at high risk for conditions that may be preventable. Aggressive monitoring for and removal of colon growths in those inheriting a gene for familial adenomatous polyposis, for example, has saved many lives. On the horizon is a gene test that will provide doctors with a simple diagnostic test for a common iron storage disease, transforming it from a usually fatal condition to a treatable one.(SEE BOX: A Twenty-first Century Diagnostic Meets a Dark Ages Treatment).

The recently commercialized gene tests for adult-onset disorders such as Alzheimer's disease and some cancers are the subject of most of the debate over
A Twenty-first Century Diagnostic Meets a Dark Ages Treatment

In the summer of 1996, researchers reported finding a gene flaw associated with hemochromatosis, a common hereditary disorder characterized by excess iron storage. Hemochromatosis appears in midlife, when the iron that has accumulated in various organs begins to wreak damage resulting in a range of problems from diabetes and cirrhosis to liver cancer and cardiac dysfunction. A simple and effective treatment has been available for centuries: excess iron is depleted through bloodletting, or phlebotomy. But diagnosis is difficult, and if the condition is left untreated, an early death will ensue. Yet when the disease is identified at an early stage, life expectancy can be normal.

Because it is one of the most common inherited diseases, and easily treated if diagnosed early (or even prevented in siblings and children of those affected), this disease stands as a model of the great potential of gene-based diagnostics.

gene testing. These tests are targeted to healthy (presymptomatic) people who are identified as being at high risk because of a strong family medical history for the disorder. The tests give only a probability for developing the disorder. One of the most serious limitations of these susceptibility tests is the difficulty of interpreting a positive result because some people who carry a disease-associated mutation never develop the disease. Scientists believe that these mutations may work together with other, unknown mutations or with environmental factors to cause disease.

A limitation of all medical testing is the possibility for laboratory errors. These might be due to sample misidentification, errors resulting from contamination of the chemicals used for testing, or other sources.

Many in the medical establishment feel that uncertainties surrounding test interpretation, current lack of available medical options for these diseases, their potential for provoking anxiety, and risks for discrimination and social stigmatization could outweigh the benefits of testing. Some complexities of current gene tests are outlined below in discussions of tests for Huntington's disease and cystic fibrosis, two disorders caused by single-gene defects, and the tests that may detect predispositions to the more complex Alzheimer's disease and breast cancer.

Huntington's Disease (HD). The test for HD costs about $275 not including the costs for doctor and genetic counseling appointments, which can run several thousand dollars. It predicts with chilling certainty the future development of this devastating neurological condition that strikes in midlife, causing progressive and unrelenting physical and mental deterioration. While taking the genetic test would help high-risk people--those with an affected parent--better plan their lives, the great majority choose not to be tested when they understand all the implications. These include the psychological impact of knowing that they will (or will not) get the disease, the absence of preventive treatments, and the risk of affecting insurance and employment status.

Cystic Fibrosis (CF). Although CF is also a single-gene disease, the issues involved in testing for mutations in this large gene are much more complex than those for HD. An astounding six hundred mutations have been found, and few correlations have been made between specific mutations and disease severity. In its most severe form, CF causes an accumulation of thick mucus in the lungs, creating an ideal breeding ground for bacteria, and damage to the gastrointestinal and reproductive systems. Someone with a mild form might have a tendency toward bronchitis.

Interpretation of a positive test is difficult, as it usually cannot predict the severity of the disease. Sometimes the disease is diagnosed in people who had no previous clue that they were "genetically ill." Another limitation of current CF gene tests is that they probe for only the most common mutations. (An example is one DNA testing company that tests for 70 CF mutations for $150.) A negative test, therefore, could not rule out CF. These limitations pose difficult quandaries for people making reproductive decisions. They gain little information in return for the costs, including social risks, involved in testing.

Early this year an independent consensus panel sponsored by the National Institutes of Health recommended that testing for CF gene mutations be offered as an option to pregnant couples and to those planning a pregnancy, as well as
to those individuals with a family history of CF and partners of people with CF. The panel did not, however, advocate testing of newborns or those in the general population. Education, counseling, and informed consent were emphasized.

**Alzheimer's Disease (AD).** Information available from the current susceptibility test for AD is even less informative. AD is a progressive brain disorder usually striking in mid- to late life and causing devastating memory loss and impaired thinking. There are two forms of AD. A rare, early-onset, simply inherited type (occurring between 35 to 60 years) accounts for about 5 percent of all cases. The much more common form of AD (sporadic AD), the subject of a controversial gene test, is a complex disease characterized by a later onset (around 70 to 80 years). Scientists believe it is caused by a combination of genes and environmental factors. The most common form of mental impairment of old age, sporadic AD now affects some four million people in the United States, and predictions are for fourteen million cases by 2040.

Researchers have found three different forms (alleles) of a gene called ApoE that appears to modify the risk of developing sporadic AD. The ApoE gene codes for a protein, called apolipoprotein E, that appears to be involved with transporting cholesterol in the blood. People with the ApoE2 allele appear to be at lowest risk of AD, those with ApoE3 have an intermediate risk, and those with ApoE4 have the highest risk.

A gene test for the ApoE alleles has been marketed to doctors since 1995 for $195. As a predictive test on healthy people, no definitive information can be gained because AD is known to develop without ApoE4, some people with ApoE4 never develop the disease, it cannot be used to predict age of onset or severity, and no current treatments or preventive methods are available. People being tested run the usual social risks concerning family and psychological issues, as well as insurance and employment discrimination. For these reasons, use of this test to predict a predisposition to AD has been discouraged by professional genetics groups.

**Breast Cancer.** Predisposition tests for people at high risk for a rare, inherited form of breast cancer have been marketed to doctors and patients since 1996. Only about 10 percent of breast cancer cases are inherited (familial). The majority are sporadic, occurring in women with no family history of the disease. This year some 185,000 U.S. women will be diagnosed with breast cancer and 44,000 will die of it. The estimated lifetime risk of breast cancer for all U.S. women (without regard to family medical history) is 12 percent by age 65. No gene tests yet exist for diagnosing or determining a susceptibility to sporadic breast cancer, but at least 50 genes have been suggested for involvement in the disease.

Mutations in two genes, called BRCA1 and BRCA2 (for BReast CAncer), have been implicated in the rare familial breast cancer. Research has suggested that women with a strong family history of the disease who carry these mutations run an increased risk of developing breast cancer, although just how much is the subject of continuing controversy. Some women with the mutations never develop breast cancer. Women with BRCA1 mutations also face a high risk of ovarian cancer compared with those in the general population. Men with BRCA1 mutations show no increased risk of breast cancer but a slightly increased risk of prostate cancer. Men with BRCA2 mutations have a slightly
higher risk of breast cancer.

Over two hundred mutations have been found in the BRCA1 and BRCA2 genes, and each family typically carries its own characteristic mutation.

The tests for BRCA1 and BRCA2 run as high as $2,400 and can involve examination of more than 16,000 DNA base pairs for mutations. Researchers say interpreting the results is very difficult, as nothing is known about the risk associated with each mutation. Also, no proven preventive or management strategies exist, so doctors do not know what follow-up to recommend. Increased surveillance, including frequent mammograms, is a possibility, but studies have not shown their usefulness in women under 50. Some women opt to remove healthy breasts (or ovaries) as a preventive measure, although there can be no assurance that all tissue has been removed. Women taking the gene tests run the usual psychological and social risks already mentioned, and these risks will very likely reach their daughters as well.

Because of profound uncertainties surrounding the breast cancer tests, their use outside the research laboratory has been discouraged by the American Society for Human Genetics and the National Breast Cancer Coalition, among others. In an editorial in *The New England Journal of Medicine* this spring, former NIH director Bernadine Healy noted that the use of the test in everyday clinical practice "violates a common-sense rule of medicine: don't order a test if you lack the facts to know how to interpret the result."

On a more optimistic note for the future, researchers are now conducting clinical trials on advanced breast, ovarian, and prostate cancer patients using the normal version of the BRCA1 gene (SEE BOX: Using Genes to Treat Disease). While this research is at a very early stage, the hope is that this and other similar trials will pave the way to completely new ways of treating previously intractable diseases and usher in an age of gene-based therapies.

**GENE-BASED MEDICINES AND GENE THERAPY FOR A NEW MILLENNIUM**

Within the next decade, researchers will find most human genes. Explorations into the function of each one --a major challenge extending far into the next century --will shed light on how faulty genes play a role in disease causation. With this knowledge in hand, commercial efforts will shift away from diagnostics and toward developing a new generation of therapeutics based on genes. Drug design will be revolutionized as researchers create new classes of medicines based on a reasoned approach using gene sequence and protein structure information rather than the traditional trial-and-error method. The drugs, targeted to specific sites in the body, will not have the side effects prevalent in many of today's medicines.

The potential for using genes themselves to treat disease--known as gene therapy--is the most exciting application of DNA science, and has captured the imaginations of the public as well as the biomedical community for good reason. This rapidly developing field holds great potential for treating or even curing genetic and acquired diseases, using normal genes to replace or supplement a defective gene or to bolster immunity to disease (e.g., by adding a gene that suppresses tumor growth). Over 150 clinical gene therapy trials are now in progress in the United States, most for different kinds of cancers. Performed on patients in advanced stages of disease, the goal of most current studies is

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**Using Genes to Treat Disease**

Researchers have taken an intriguing step toward developing new treatments for breast, ovarian, and prostate cancers. Last year, reports demonstrated that injecting a normal version of the BRCA1 gene could stop unwanted cell growth and inhibit tumor growth when introduced into human tumors grafted onto lab mice. Researchers are now testing the effects of injecting a normal BRCA1 gene into women with advanced breast and ovarian cancer and men with prostate cancer; this type of treatment is called gene therapy. 
The goal of these and most current gene-therapy studies is not yet therapeutic; their primary objectives are to demonstrate safety of the procedure, not its efficacy.

establishing the safety of gene therapy rather than its effectiveness. The technology itself still faces many obstacles before it can become a practical approach for treating disease.

The atlas of human biology generated by the HGP will provide an enormous store of genes for studying, and ultimately preventing, the ills that beset us. As the factors underlying the maladies and vagaries of the human condition slowly come to light, the challenge will be to use the information responsibly.

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