

**GENOMES** to  
**LIFE**  
ACCELERATING  
BIOLOGICAL  
DISCOVERY

U.S. DEPARTMENT OF ENERGY

**Black Bag**

Spring 2002

# The Human Genome Project: Sequencing the Future

In 1986, the U.S. Department of Energy (DOE), convinced that its mission would be well served by a comprehensive picture of the human genome, took a bold and unilateral step by announcing its Human Genome Initiative—forerunner of the Human Genome Project. The immediate response was considerable skepticism about the technological capability to sequence the genome at a reasonable cost and even about the value of the result, if it could be obtained economically.

Over a decade later, genome technologies and data are revolutionizing biology and providing a vital thrust to the increasingly broad scope of the biological sciences. Researchers have completed a rough draft of the human genome, with the high-quality finished version scheduled for completion by 2003. In addition to this major accomplishment, an array of newly completed model-organism genome sequences provides a useful tool for performing comparative studies that provide a better understanding of the human genome and a more comprehensive understanding of complex living systems. The expected impact on medicine and health care alone is inestimable. The growing knowledge base will also find a host of practical applications in many other critical areas, including those important to DOE missions.

The Human Genome Project and DOE's complementary genome programs—Genomes to Life, the Microbial Genome Program, and the Microbial Cell Project—ultimately will lead to the production of plentiful and cleaner energy resources that will help stabilize atmospheric carbon dioxide to counter global warming and ensure U.S. energy security by reducing our dependence on fossil fuels. The new findings also have the potential to provide tools for enhanced biothreat agent detection and response and for using genetically engineered microbes to clean up toxic wastes in contaminated sites.

Even as the HGP began in 1986, project managers, researchers, and lawmakers recognized that the increasing knowledge about human biology and personal genetic information, as well as new capabilities for manipulating the genetic material of other organisms, would raise a number of complex societal issues. In response to congressional mandates, DOE and NIH continue to devote a portion of their annual HGP budgets to identifying and addressing the project's ethical, legal, and social implications (ELSI).

Now the world's largest bioethics undertaking, the ELSI component has become a model for others around the world and, nationally, has led to similar endeavors in related research areas. HGP ELSI programs emphasize the privacy of genetic information, its safe and effective introduction into the clinical setting, fairness in its use, and professional and public education. The programs focus on ethical, legal, cultural, social, and psychological consequences that could affect policy development and service delivery.

We have thus far seen only the dawn of the biological revolution. The practical and economic applications of biology are destined for dramatic growth. Still far from reaching its potential, health-related biotechnology is already a multibillion-dollar success story. Other applications of biotechnology are likely to beget similar successes in the coming decades.

The insights, technologies, and infrastructure already emerging from genome projects, together with research advances in fields such as computational and structural biology and ELSI, are among our most important tools for addressing many national needs.

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# The Human Genome Project Partners with Minority Community Leaders for Genomics Education



The Human Genome Programs of the U.S. Department of Energy (DOE) Office of Biological and Environmental Research and the National Human Genome Research Institute of the National Institutes of Health devote 3% and 5% of their annual budgets, respectively, toward studying the ethical, legal, and social issues (ELSI) surrounding avail-

ability of personal genetic information. Some of these projects examine potential ELSI concerns, and others seek to educate professionals and the public through literature, conferences, workshops, and multimedia. Among the programs funded by these ELSI programs are educational materials and programs for physicians and other medical professionals, educators, students, clergy,

and judges and other legal professionals.

One of these programs is a partnership with the National Educational Foundation of Zeta Phi Beta Sorority, Inc., which has committed itself to informing minority communities about the Human Genome Project (HGP), its benefits, and potential societal implications. The sorority planned and con-



*Pictured left-right: Dr. Kathryn Malvern, Chair of the National Educational Foundation, Zeta Phi Beta Sorority, Inc.; Dr. Ari Patrinos, Director of the DOE Human Genome Program; Issie L. Jenkins, Esq., Chair of the National Educational Foundation Board of Managers, Zeta Phi Beta Sorority, Inc., and Dr. Dan Drell, Manager of the Ethical, Legal, and Social Issues component of the DOE Human Genome Program.*

ducted four major informational conferences on the HGP and its impact on minority communities. The conferences covered a variety of topics from basic

genetics and HGP history to gene testing and careers in genetics. Held in Washington DC, and Atlanta in 2001, Philadelphia in 2000, and New Orleans

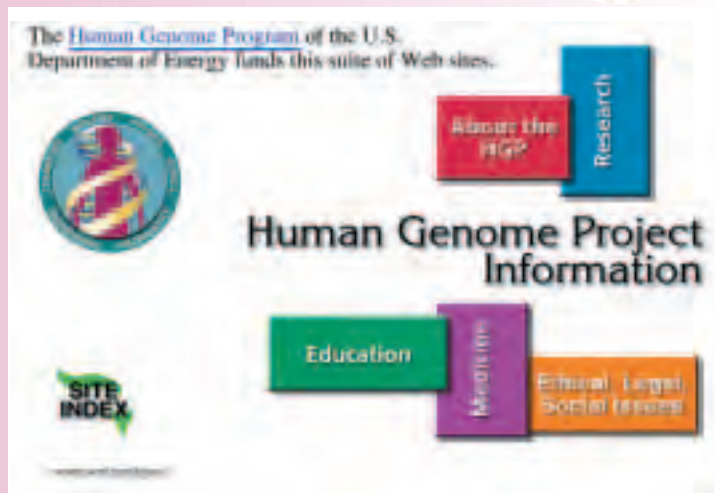
in 1999, these conferences sparked numerous follow-up meetings and training sessions led by members of the educational foundation. [Proceedings of the 2000 conference: [www.ornl.gov/hgmis/publicat/zetaphibeta/](http://www.ornl.gov/hgmis/publicat/zetaphibeta/)]

In 1996, the Human Genome Project collaborated with Tuskegee University and other funding agencies to present the 3-day conference, "Plain Talk About the Human Genome Project." The conference brought together internationally recognized scientists, bioethicists, and legal scholars from government, indus-

## *The Human Genome Project Information Suite of Web Sites*

The Human Genome Project Information Suite of Web sites offers a unique compilation of text, downloadable images and presentations, and links that cover all aspects of the project and many of the medical, technological, and societal ramifications of genome research. Because applications of genomics are becoming so pervasive in all sectors of society, HGPI strives to present this information in language understandable to a broad audience that includes the general public as well as scientists, social scientists, and medical and legal practitioners, among others. An interactive feature allows the visitor to ask questions on genomics research and its societal impacts. Praised by the journal *Science* as "possibly the best single

resource for those new to genetics and genomics," HGPI web pages include primers, fact sheets, progress reports, and the newsletter *Human Genome News*.





try, and academia. In rare “both-sides-of-the-argument” discussions, speakers expressed apprehension about the project and the use of its resulting genetic information. Concerns ranged from the fear of actuarial classifications of “genetic exceptionalism” to the burden faced by African Americans if they were among those labeled by some as a biological underclass. Focused particularly on how the data might affect African Americans, the meeting also was a vehicle for students from Tuskegee and other historically black institutions to meet with genome scientists, hear the issues, and explore career possibilities in genomics. Proceedings from this conference are

available as a book, *Plain Talk About the Human Genome Project*, 292 pp., 1997. [Ordering Information: <http://agriculture.tusk.edu/caens/genome/genome.html>]

About 150 leaders of minority communities came together in June 1997 at the University of Maryland, Baltimore, to learn about the HGP. Partially sponsored by the DOE and the NIH, the meeting's goals were to (1) inform minority communities about the HGP by explaining its potential benefits and clarifying its possible ELSI implications; and (2) make known the aspirations and interests of these communities to genome project scientists and policy-makers. This program grew from organ-

izers' concerns about an information vacuum among minorities regarding the genome project and the possibility that suspicions would arise about the project's intent.

Proceedings from this conference and other added material form the book, *The Human Genome Project and Minority Communities: Ethical, Social, and Political Dilemmas*, edited by Raymond Zilinskas (Monterey Institute of International Studies) and Peter Balint (University of Maryland), 144 pp., 2000. It addresses the divisions between minority groups and the scientific community, particularly in medical and genetic research [available through bookstores, including online suppliers].

## From the Genome to the Proteome: A Short Primer

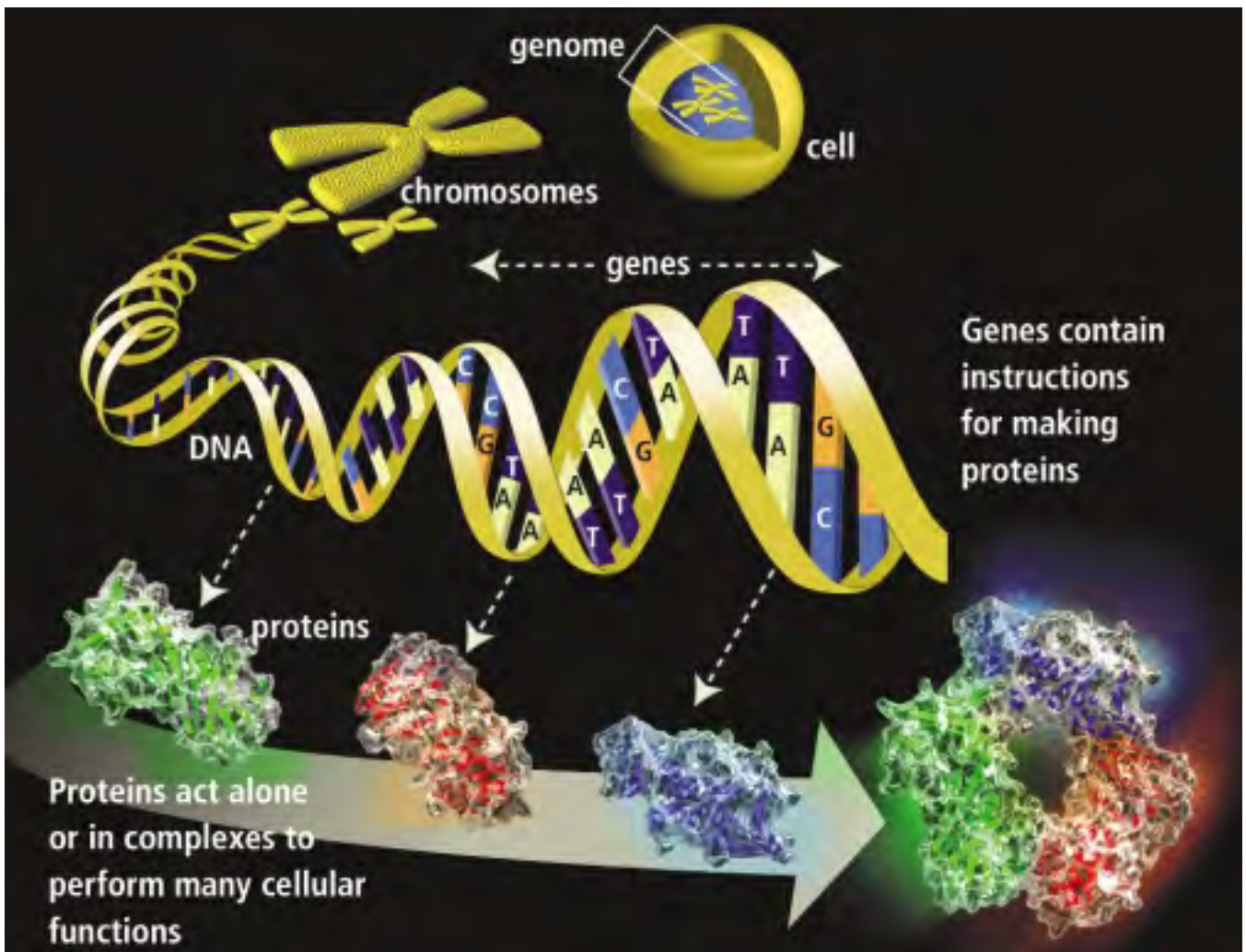
**C**ells are the fundamental working units of every living system. All the instructions needed to direct their activities are contained within the chemical **DNA** (deoxyribonucleic acid). DNA from all organisms is made up of the same chemical and physical components. The DNA sequence is the particular side-by-side arrangement of bases along the

DNA strand (e.g., ATTCCGGA). This order spells out the exact instructions required to create a particular organism with its own unique traits.

The **genome** is an organism's complete set of DNA. Genomes vary widely in size: the smallest known genome for a free-living organism (a bacterium) contains about 600,000 DNA base pairs, while human and mouse genomes

have some 3 billion. Except for mature red blood cells, all human cells contain a complete genome.

DNA in the human genome is arranged into 24 distinct **chromosomes**—physically separate molecules that range in length from about 50 million to 250 million base pairs. A few types of major chromosomal abnormalities, including missing or



## *Working Draft vs Finished Sequence: What's the Difference?*

In 2001, scientists from the public Human Genome Project and the private company Celera Genomics published the long-awaited details of the working draft of the human genome.

In generating the draft sequence, scientists determined the order of base pairs in each chromosomal area at least 4 to 5 times (4x to 5x) to ensure data accuracy and to help with reassembling DNA fragments in their original order. This repeated sequencing is known as genome "depth of coverage." Draft sequence data are mostly in the form of 10,000 base-pair-sized fragments whose approximate chromosomal locations are known.

To generate high-quality sequence, additional sequencing is needed to close gaps, reduce ambiguities, and allow for only a single error every 10,000 bases, the agreed-upon standard for HGP finished sequence. Investigators believe that a high-quality sequence is critical for recognizing regulatory components of genes that are very important in understanding human biology and such disorders as heart disease, cancer, and diabetes.

The finished version, expected by 2003, will provide an estimated 8x to 9x coverage of each chromosome. Thus far, finished sequences have been generated for only three human chromosomes—20, 21, and 22.

extra copies or gross breaks and rejoinings (translocations), can be detected by microscopic examination. Most changes in DNA, however, are more subtle and require a closer analysis of the DNA molecule to find perhaps single-base differences.

Each chromosome contains many genes, the basic physical and functional units of heredity. **Genes** are specific sequences of bases that encode instructions on how to make proteins, the molecules that perform most life functions and even make up the majority of cellular structures. Genes comprise only about 2% of the human genome; the remainder consists of non-coding regions, whose functions may include providing chromosomal structural integrity and regulating where,

when, and in what quantity proteins are made. The human genome is estimated to contain 30,000 to 40,000 genes.

Although genes get a lot of attention, it's the proteins that perform most life

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functions. **Proteins** are large, complex molecules made up of smaller subunits called amino acids. Chemical properties that distinguish the 20 different amino acids cause the protein chains to fold up into specific three-dimensional

structures that define their particular functions in the cell.

The constellation of all proteins in a cell is called its **proteome**. Unlike the relatively unchanging genome, the dynamic proteome changes from moment to moment in response to tens of thousands of intra- and extra-cellular environmental signals. A protein's chemistry and behavior is specified by the gene sequence and by the number and identities of other proteins made in the same cell at the same time and with which it associates and reacts. Studies to explore protein structure and their activities, known as proteomics, will be the focus of much research for decades to come and will help elucidate the molecular basis of health and disease.



# The Human Genome Project

## A Little Bit of History

Though surprising to many, the Human Genome Project (HGP) traces its roots to an initiative in the U.S. Department of Energy (DOE). Since 1945, DOE and its predecessor agencies have been charged by Congress with developing new energy resources and technologies and with pursuing a deeper understanding of potential health and environmental risks posed by their production and use. Such studies have since provided the scientific basis for individual risk assessments of

nuclear medicine technologies, for example.

In 1986, DOE took a bold step in announcing its Human Genome Initiative, convinced that DOE's missions would be well served by a reference human genome sequence. Shortly thereafter, DOE and the National Institutes of Health developed a plan for a joint HGP that officially began in 1990.

## Ambitious Goals . . .

From the outset, the HGP's ultimate goal has been to generate a high-quality

reference sequence for the entire human genome and identify all human genes. Other important goals are to sequence the genomes of model organisms to help interpret human DNA, enhance computational resources to support future research and commercial applications, and explore gene function through comparative mouse-human studies. The sequence is a magnificent and unprecedented resource that will serve as a basis for research and discovery throughout this century and beyond. Potential applications are





## Building on the HGP: Genomes to Life

Today, scientists have in hand the complete DNA sequences of many organisms--from microbes to mice to humans. For the first time, they can begin to explore the "operating systems" of life written into these genetic codes and put them to use. At the leading edge of this great scientific frontier is the DOE Genomes to Life program, whose overarching goal is to use these biological tools to target critical DOE mission challenges.

Future applications of this knowledge promise far-reaching benefits to the nation:

- Independence from foreign oil
- Enhanced biowarfare agent detection and response
- Stabilization of atmospheric carbon dioxide to counter global warming

- Significant savings in toxic waste cleanup and disposal

Genomes to Life will build on the Human Genome Project, both by exploiting its data and by extending the whole-genome approach to attaining a comprehensive understanding of how entire biological systems work. This will lead to models that enable scientists to understand living systems well enough to predict their behavior under different environmental conditions. Applications of this level of understanding will be revolutionary.

For more information, see [doegenomesto-life.org](http://doegenomesto-life.org).



numerous and include customized medicines, improved agriculture products, new energy resources, and tools for environmental cleanup.

The HGP also aims to train future scientists, study human variation, and address critical societal issues arising from the increased availability of personal human genome data and related analytical technologies.

### ...And Exciting Progress

Although the HGP originally was

planned to last 15 years, rapid technological advances and worldwide participation have accelerated the expected completion date to 2003. In June 2000 scientists announced biology's most stunning achievement: the generation of a working draft sequence of the entire human genome. In addition to serving as a scaffold for the finished version, the draft provides a road map to an estimated 90% of genes on every chromosome and already has enabled gene hunters to pinpoint genes associated

with over 30 disorders.

HGP resources have spurred a boom in spin-off sequencing programs on the human and other genomes in both the private and public sectors. To stimulate further research, all data generated in the public sector are made available rapidly and free of charge via the Web. Details of the draft sequence, as reported in *Nature* (Feb. 15, 2001) and *Science* (Feb. 16, 2001), are on the Web ([www.ornl.gov/hgmis/project/journals/journals.html](http://www.ornl.gov/hgmis/project/journals/journals.html)).

## The Next Step: Functional Genomics

The words of Winston Churchill, spoken in 1942 after 3 years of war, capture well the HGP era: "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

The avalanche of genome data grows daily. The new challenge will be to use this vast reservoir of data to explore how DNA and proteins work with each other and the environment to create complex, dynamic living systems. Systematic studies of function on a

grand scale—functional genomics—will be the focus of biological explorations



in this century and beyond. These explorations will encompass studies in

transcriptomics, proteomics, structural genomics, new experimental methodologies, and comparative genomics.

- **Transcriptomics** involves large-scale analysis of messenger RNAs transcribed from active genes to follow when, where, and under what conditions genes are expressed.
- Studying protein expression and function—or **proteomics**—can bring researchers closer to what's actually happening in the cell than gene-expression studies. This capability has applications to drug design.

### *Whose Genome is It?*

In the Human Genome Project, researchers collected blood (female) or sperm (male) samples from a large number of donors. Only a few samples were processed, with the source names protected so neither donors nor scientists knew whose DNA was being sequenced. The reference sequence will be applicable to everyone because all humans share the same basic set of genes and genomic regulatory regions that control the development and maintenance of their biological structures and processes. In studies of DNA variations among individuals (0.1% of our genomes), researchers in both public and private sectors have developed DNA resources from many representative population groups.



### ***Bioinformatics Boom: Managing the Data***

Massive quantities of genomic data and high-throughput technologies are now enabling studies on a vastly larger scale than ever before, for example, in monitoring and comparing the activity of tens of thousands of genes simultaneously in cancerous and noncancerous tissue. Advanced computational tools and interdisciplinary experts are needed to capture, represent, store, integrate, distribute, and analyze all the data.

Bioinformatics is the term coined for the new field that merges biology, computer science, and information technology to manage and analyze the data, with the ultimate goal of understanding and modeling living systems. Computing and information demands will continue to rise with the explosive torrent of data from large-scale studies at the molecular, cellular, and whole-organism levels. [Tour the public DNA sequence database GenBank: [www.ncbi.nlm.nih.gov/Tour/](http://www.ncbi.nlm.nih.gov/Tour/)]



- **Structural genomics** initiatives are being launched worldwide to generate the 3-D structures of one or more proteins from each protein family, thus offering clues to function and biological targets for drug design.
- **Experimental methods** for understanding the function of DNA sequences and the proteins they encode include knockout studies to inactivate genes in living organisms and monitor any changes that could reveal their functions.
- **Comparative genomics**—analyzing DNA sequence patterns of humans and well-studied model organisms side-by-side—has become one of the most powerful strategies for identifying human genes and interpreting their function.

## Medicine and the New Genetics: Gene Testing, Pharmacogenomics, and Gene Therapy

**D**NA underlies every aspect of our health in function and dysfunction. Obtaining a detailed picture of how genes and other DNA sequences function together and interact with environmental factors ultimately will lead to the discovery of pathways involved in normal processes and in disease pathogenesis. Such knowledge will have a profound impact on the way disorders are diag-

nosed, treated, and prevented and will bring about revolutionary changes in clinical and public health practice. Some of these transformative developments are described below.

### Gene Tests

DNA-based tests are among the first commercial medical applications of the new genetic discoveries. Gene tests can be used to diagnose disease, confirm a

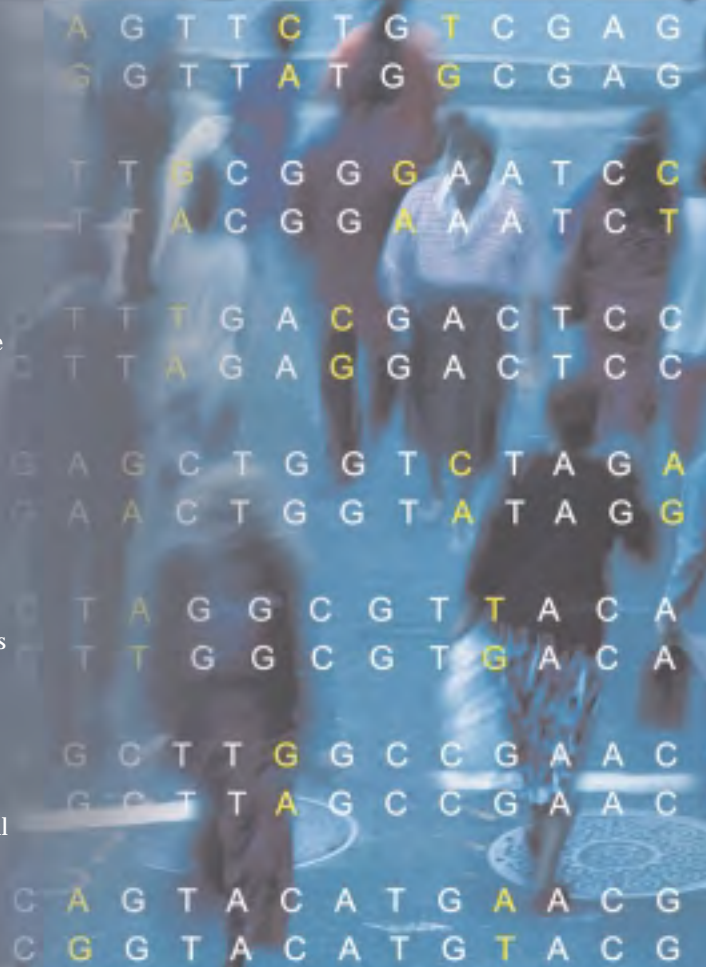
diagnosis, provide prognostic information about the course of disease, confirm the existence of a disease in asymptomatic individuals, and, with varying degrees of accuracy, predict the risk of future disease in healthy individuals.

Currently, several hundred genetic tests are in clinical use, with many more under development, and their numbers and varieties are expected to increase rapidly over the next decade. Most cur-

### *SNPing the Human Genome*

Slight variations in our DNA sequences can have a major impact on whether or not we develop a disease and on our particular responses to such environmental insults as bacteria, viruses, and toxins. They also impact our reactions to drugs and other therapies. One of the most common types of sequence variation is the single nucleotide polymorphism (SNP). SNPs are sites in the human genome where individuals differ in their DNA sequence, often by a single base. For example, one person might have the base A (adenine) where another might have C (cytosine), and so on.

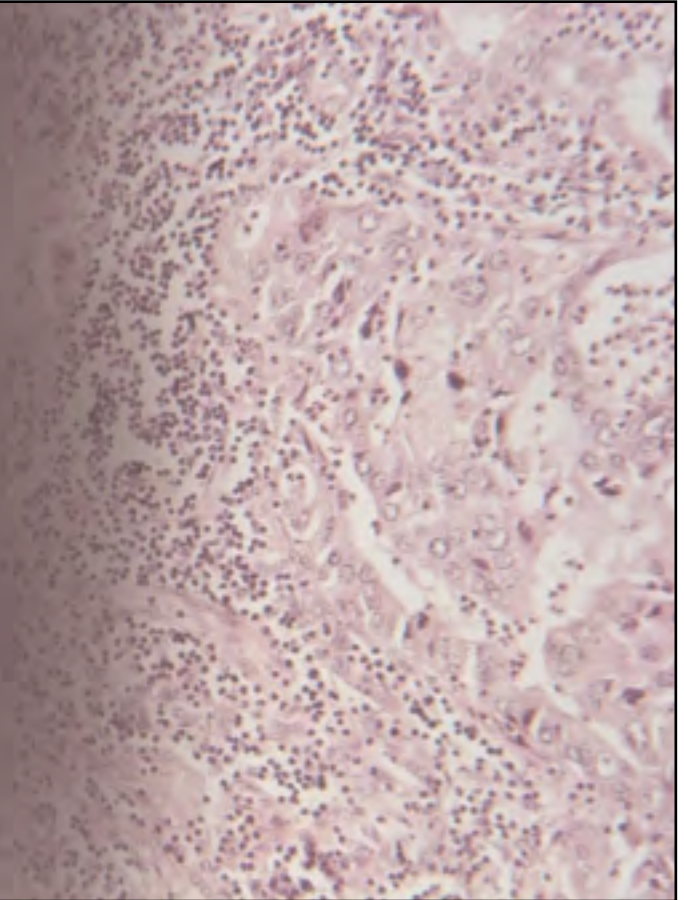
Researchers in public and private sectors are generating maps of these sites, which can occur in genes as well as in noncoding regions. Scientists believe such SNP maps will help them identify the multiple genes associated with such complex diseases as cancer, diabetes, vascular disease, and some forms of mental illness. SNP maps provide valuable targets for biomedical and pharmaceutical research.



## *Cancer and the Genome*

Some experts believe that genomic technologies will transform cancer diagnosis and treatment in the next two decades, with the first breakthroughs bringing life-prolonging therapies for difficult-to-treat malignancies. Promising developments include the ability to quickly detect a cancer-related gene signaling the presence of micrometastases—difficult-to-detect tumor cells in lymph nodes that indicate the spread of cancer. Such new tests may eliminate additional surgeries by detecting the presence of rare tumor cells often missed by conventional microscopic evaluations during surgery.

Future developments in cancer treatment probably will be based on specific gene-expression "fingerprints" of tumors and the therapies tailored to those patterns. Toward this end, the Cancer Genome Anatomy Project of the National Cancer Institute is determining the gene-expression profiles of normal, precancer, and cancer cells, with the goal of improving detection, diagnosis, and treatment. [<http://cgap.nci.nih.gov>]



rent tests detect mutations associated with rare genetic disorders that follow Mendelian inheritance patterns. These include myotonic and Duchenne muscular dystrophies, cystic fibrosis, neurofibromatosis type 1, sickle cell anemia, and Huntington's disease.

Recently, tests have been developed to detect mutations for a handful of more complex conditions such as breast, ovarian, and colon cancer. Although they have limitations, these tests sometimes are used to make risk estimates in presymptomatic individuals with a family history of the disorder.

One potential benefit to using these gene tests is that they could pro-

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vide information that helps physicians and patients manage the disease or

condition more effectively. Regular colonoscopies for those with mutations associated with colon cancer, for instance, could prevent thousands of deaths each year.

Some scientific limitations are that the tests may not detect every mutation associated with a particular condition (because many are as yet undiscovered), and the ones they do detect may present different risks to people and populations. Another important consideration is the lack of effective treatments or preventive measures for some diseases and conditions now

## *Twenty-First Century Diagnostics Meets 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 typically 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 for gene-based diagnostics.

being diagnosed or predicted.

Revealing information about risk of future disease can have significant emotional and psychological effects as well. The absence of privacy and antidiscrimination protections can lead to discrimination in employment or insurance or other misuse of personal genetic information. Additionally, because genetic tests reveal information about individuals and their families, test results can affect family dynamics. Results also can pose risks for population groups if they lead to group stigmatization.

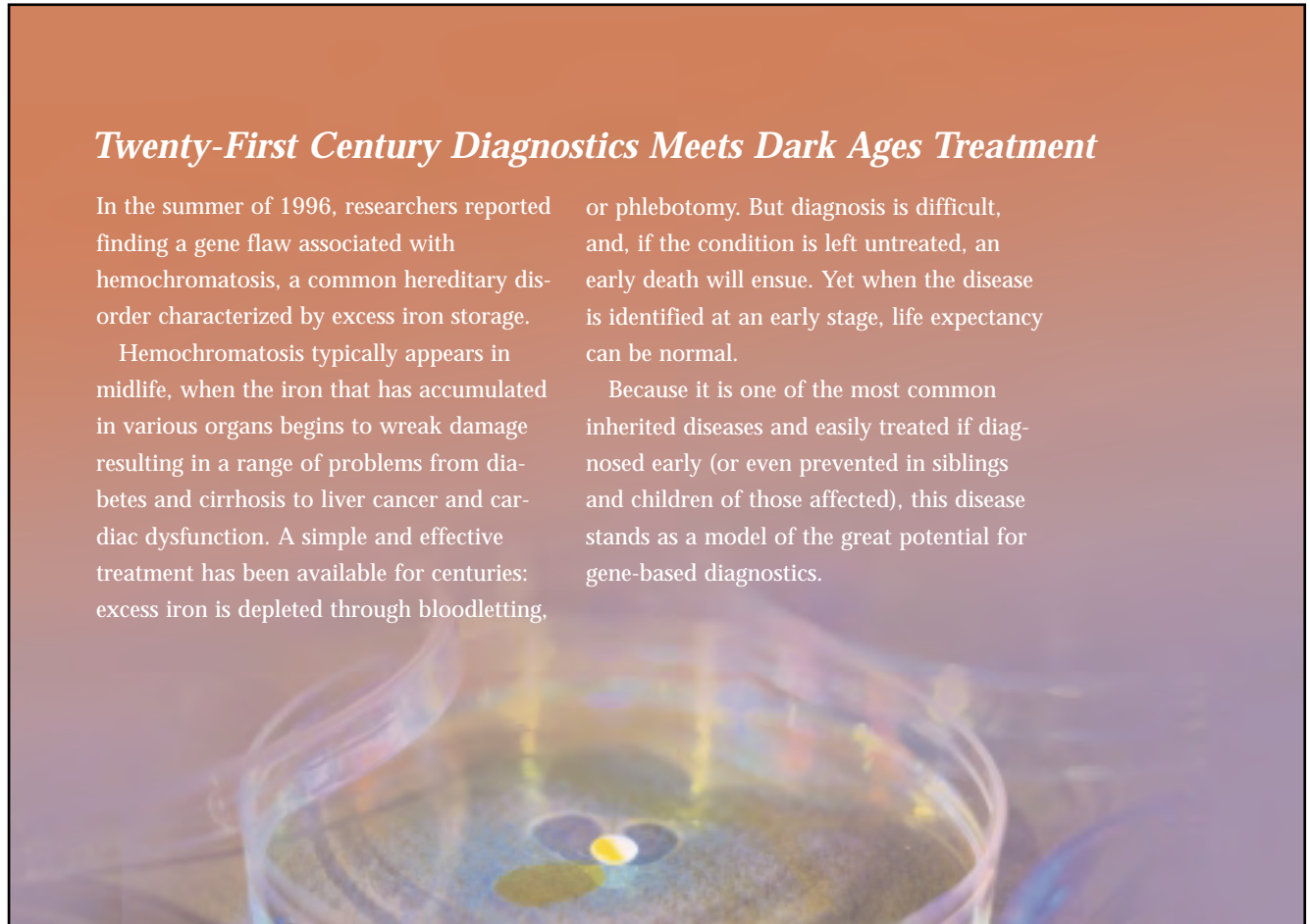
Other issues related to gene tests include their effective introduction into clinical practice, the regulation of laboratory quality assurance, the availability of testing for rare diseases, and the education of healthcare providers and patients about correct interpretation and attendant risks.

### **Pharmacogenomics: Moving Away From "One-Size-Fits-All" Therapeutics**

Within the next decade, researchers will begin to correlate DNA variants

(SNPs, see sidebar on page 10) with individual responses to medical treatments, identify particular subgroups of patients, and develop drugs customized for those populations. This new field blending pharmacology with new genomics capabilities is known as pharmacogenomics.

Over a hundred thousand people die each year as the result of adverse responses to medications that are beneficial to others, and another 2.2 million experience serious reactions. Variation in drug response ranges from failure to respond at all to adversely reacting to



one or multiple drugs. DNA variants in genes involved in drug metabolism, particularly the cytochrome P450 multi-gene family, are the focus of much current research in this area. Enzymes encoded by these genes are responsible for the metabolism of most drugs used today, including many for treating psychiatric, neurological, and cardiovascular diseases. Enzyme function affects patients' responses to both the drug and the dose. Future advances will enable rapid testing to determine the patient's genotype and drastically reduce hospital-

ization due to poor reactions.

Genomic data and technologies also are expected to make drug development faster, cheaper, and more effective. Most drugs today are based on about 500 molecular targets; genomic knowledge of genes involved in diseases, disease pathways, and drug response sites will lead to the discovery of thousands of new targets. New drugs, aimed at specific sites in the body and at particular biochemical events leading to disease, probably will cause fewer side effects than many current

medicines. Ideally, the new genomic drugs could be given earlier in the disease process. As knowledge becomes available to select patients most likely to benefit from a potential drug, pharmacogenomics will speed the design of clinical trials to bring the drugs to market sooner.

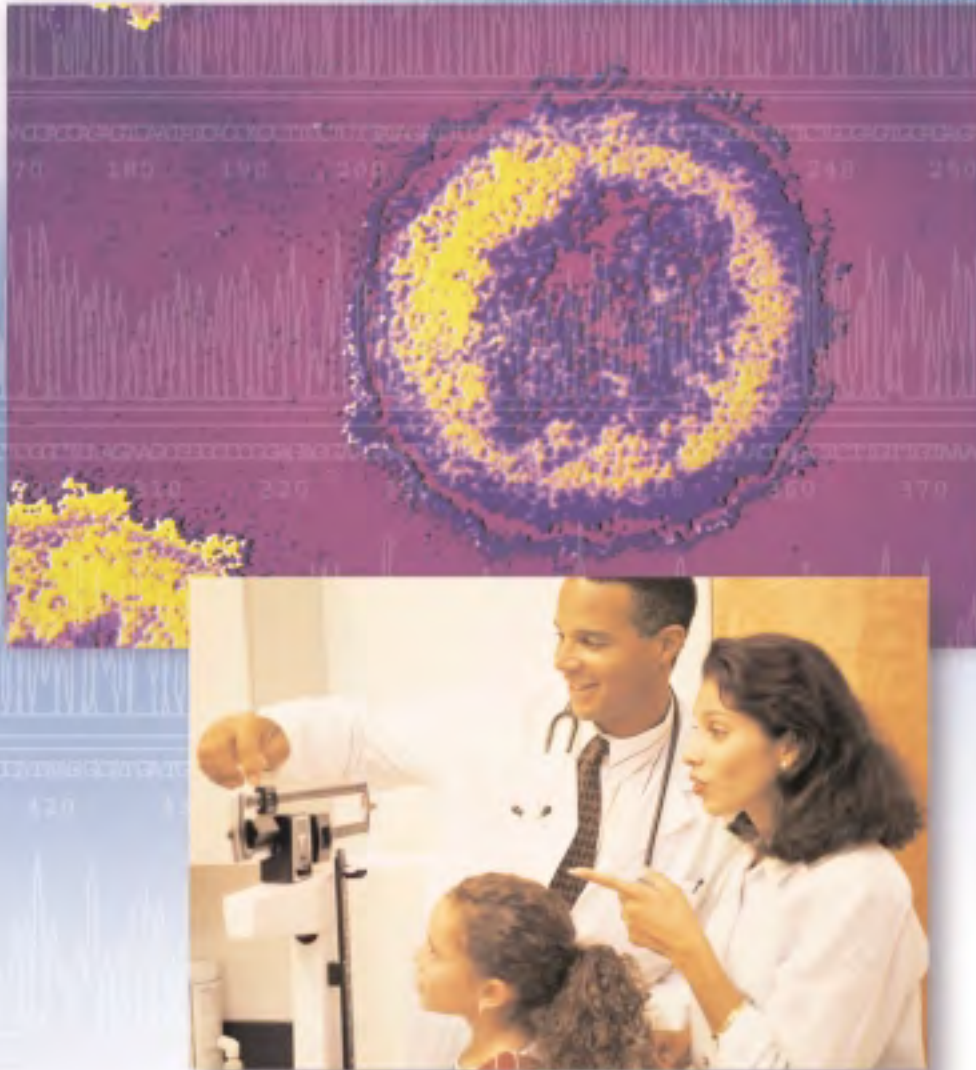
### Gene Therapy and Enhancement

The potential for using genes themselves to treat disease or enhance particular traits has captured the imagination of the public and the biomedical

### *Cheating the Fates: Making Healthy Babies Through Science*

Several in vitro fertilization (IVF) clinics offer prospective parents who are at high risk for some genetic diseases (such as Tay Sachs and Huntington's disease) a way to ensure that they will not pass on the defective gene to their children. The clinics also offer them the option of remaining ignorant of their own genetic status, which many choose. After fertilization of the egg outside the mother's body, scientists test resulting embryos for gene mutations associated with a particular disease, and embryos without the mutation are selected preferentially for uterine implantation.





community. This largely experimental field—gene transfer or gene therapy—holds potential for treating or even curing such genetic and acquired diseases as cancers and AIDS by using normal genes to supplement or replace defective genes or bolster a normal function such as immunity.

Over 500 clinical gene-therapy trials involving about 3500 patients have been identified worldwide. The vast majority (78%) take place in the United States, followed by Europe (18%). Most trials focus on various types of cancer,

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although monogenic, infectious, vascular, and other multigenic diseases are being studied as well. Protocols gener-

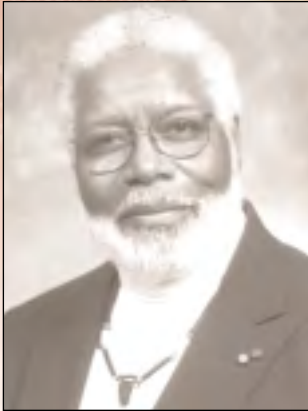
ally are aimed at establishing the safety of gene-delivery procedures rather than effectiveness, and no cures as yet can be attributed to these trials.

Gene transfer still faces many scientific obstacles before it can become a practical approach for treating disease. According to the American Society of Human Genetics' Statement on Gene Therapy, effective progress will be achieved only through continued rigorous research on the most fundamental mechanisms underlying gene delivery and gene expression in animals.



# Historical Perspective: The Sickle Cell Testing Debacle

by Robert Murray, Jr., MD



Robert  
Murray, Jr.,  
MD



In the 1970s, a major effort was made in many states, with federal government support, to screen African-American children and young adults for the mutation associated with sickle cell disease. Many of the screening programs were based on inadequate knowledge of the genetics of the disease, and, in some instances, the accuracy and validity of the test itself was in question. Also, many programs were implemented without sufficient sensitivity to ethnocultural issues and the potential for misuse of personal test results. Individuals who were actually carriers of the mutation were incorrectly identified as having sickle cell disease. These individuals were ostracized, deprived of employment and educational opportunities, and denied health and life insurance.<sup>1</sup>

This article about the sickle cell testing debacle is adapted from "The Ethics of Predictive Genetic Screening: Are the Benefits Worth the Risks?" presented by Robert Murray, Jr., M.D., at the 1996 Tuskegee University Conference on the Human Genome Project. Dr. Murray is Chief of the Division of Medical Genetics, Department of Pediatrics and Child Health; and Professor of Pediatrics, Medicine, and Genetics at Howard University in Washington, D.C.

<sup>1</sup> Introductory paragraph is adapted from the Secretary's Advisory Committee on Gene Testing's document, *Public Consultation on Oversight of Genetic Tests* (<http://www4.od.nih.gov/oba/sacgt.htm>).

I am going to tell a story about testing for the sickle cell trait—the disease but the carrier state. This story may be a harbinger of what we might encounter on a much larger scale with the growth of various genetic tests for genetic conditions and susceptibilities.

In 1970, sickle cell disease was rediscovered, in a sense. Some physi-

cians realized that there was considerable knowledge about the structure and function of the sickle cell gene, but little was being done with this informa-

tion.

A report in the *New England Journal of Medicine* caused a tremendous furor over the possibility that carrying

even a single copy of the gene associated with sickle cell was dangerous. Of course, had that been the case, we would have seen thousands of Africans

## ***Sickle Cell Anemia Quick Facts***

### **What is sickle cell anemia?**

Sickle cell anemia, a group of red blood cell disorders, causes chronic anemia, episodes of pain, and eventually death. It is the most common genetic disease in the United States, affecting at least 70,000 Americans, including about 1 in 375 African Americans and 1 in 1000 to 1400 Hispanic Americans. With an incidence of 8 in 100,000 people, it is found in almost all populations around the world but is most prevalent in people whose ancestors lived in malaria-infested areas. The mutation is thought to have originated thousands of years ago in West Africa, where it serves as a protection against malaria.

The three most common types of sickle cell disease in the United States are hemoglobin SS or sickle cell anemia, hemoglobin SC disease, and hemoglobin sickle beta-thalassemia. In sickle cell anemia, a mutation in the gene coding for the hemoglobin protein causes normally disc-shaped red blood cells to become crescent shaped, stiff, and distorted. They have difficulty passing through the body's small blood vessels, causing severe pain as well as strokes and damage to bones and tissues that do not receive adequate blood flow. Repeated crises also can damage the eyes, kidneys, lungs, and liver. Death can occur if red blood cells break down or bone marrow fails to produce blood cells (aplastic anemia).

### **Who gets sickle cell anemia?**

Sickle cell anemia affects only individuals who inherit hemoglobin S from both parents. Sickle cell trait, which usually causes no or only mild symptoms, results from inheriting hemoglobin S from one parent and normal hemoglobin (A) from the other. Parents who are both carriers have a one in four chance of having an unaffected child, one in four for a child with sickle cell disease, and one in two for a child with sickle cell trait.

### **What kind of treatment is available?**

Early detection is important so affected individuals can begin treatment before they show debilitating symptoms, and testing for sickle cell disease has improved greatly over the past two decades. Newborn screening, required in many states, allows babies to be placed on oral antibiotics at the age of 4 months to protect against often-fatal overwhelming infections. Due to this and other improvements in therapy, the death rate is decreasing steadily and life expectancy is increasing.

*Normal red blood cells*

*Sickled blood cells*

dying, because in some places 30% to 40% of the population may carry the sickle cell trait.

Additionally, the sickle cell trait was thought to be responsible for the sudden unexpected deaths of four army recruits during extreme exercise. The National Academy of Sciences convened a special committee funded by the Department of Defense, which was concerned about African-American armed services personnel who might have the sickle cell trait. The finding of the committee, which I happened to chair, was that there was no clear association between the trait and the deaths. Recruits who actually had the disease, however, were getting past the medical examinations and into the military. We suggested testing to keep them out.

Two years later, President Nixon recommended that \$6 million be spent for sickle cell research. The National Sickle Cell Anemia Control Act was enacted, and African Americans got very excited about these events. Sickle cell screening began all over the country, using a very simple test that required no laboratory skill whatsoever. The trouble was that the test did not distinguish between the sickle cell trait and the disease, so many people who had a positive result thought they had sickle cell anemia. Consequently, this caused a tremendous amount of anxiety in the African-

American community.

At the same time, the National

**The first  
breakthrough  
supporting genetic  
screening for  
sickle cell came  
about when  
prophylactic  
penicillin was  
found to reduce  
mortality and  
morbidity in  
sickle cell  
anemic infants.**

Institutes of Health (NIH) established some comprehensive sickle cell research centers through the National Heart, Lung, and Blood Institute, and mass screening programs were initiated without sufficient public education. People thought there must be an epidemic of sickle cell disease, and some thought it was communicated sexually. You can imagine the confusion that reigned because the public and many members of the medical profession were largely uneducated about the true significance of the tests. At that time, no safe prenatal diagnostic test was

available for a couple who both were carriers, so their only option was to avoid having children. Some even concluded that this might be a genocidal program—a way of keeping black people from having babies.

More sickle cell centers were established and a massive national education program was begun, but not before some states enacted laws to require mandatory testing for the sickle cell trait. All or most of these laws were proposed by black legislators who thought they were doing something positive for their black constituents. Fortunately, at the time the educational program began, some citizens launched legal suits to block such testing because it was mandatory for blacks but not for whites.

In 1975 other disease-oriented groups became aware that lots of money was being spent for sickle cell





programs. Thalassemia, hemophilia, and various other special-interest disease groups wanted their pieces of the federal pie. An omnibus genetics bill was introduced that set model standards and a rationale for genetic screening programs.

Other negative effects came from being identified as a carrier of the sickle cell gene. Psychological distress caused chest and abdominal pain in some children, and their mothers thought they were experiencing a sickle cell crisis. The supposed connection between exercise and sudden death meant that black kids all over the coun-

try were required to be tested for sickle cell trait before they could go out for sports, and their parents had to sign waivers. This policy unnecessarily excluded a lot of young people from participating in athletics. Discriminatory laws that mandated sickle cell testing were carried out, and school kids were stigmatized.

About that time Dr. James Neel, who was considered one of the fathers of human population genetics and whose word carried a lot of weight, gave a paper in which he suggested that the life expectancy for an individual with sickle cell trait was 5% shorter than

that of the average person. This led several insurance companies to increase life insurance premiums for those individuals. The increase was rescinded later when other studies did not support Dr. Neel's findings.

Selective screening of blacks in industrial settings led to carriers of the sickle cell trait being excluded from "high-risk" jobs. They also were kept from being pilots, not only in commercial airlines but in the U.S. Air Force Academy. This limitation has been modified recently but not eliminated. Some black flight attendants who were carriers were terminated from their jobs even

## *Some of the Most Common Single-Gene Disorders*

Over 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.

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, schizophrenia, and manic depression are all examples of complex diseases.

Some examples of disorders caused by mutations in a single gene are:

- Congenital heart defects (encompasses a variety of malformations)
- Familial adenomatous polyposis (colon cancer)
- Polycystic kidney disease
- Hemochromatosis (iron storage disease)
- Neural tube defects

- Hypercholesterolemia
- Diabetes, type 1
- Breast and ovarian cancer
- Cleft lip and palate
- Down Syndrome
- Fragile-X mental retardation
- Sickle cell anemia
- Cystic fibrosis
- Duchenne Muscular Dystrophy
- Hemophilia A
- Marfan Syndrome



though they had been flying for years without any ill effects. This is only a partial list of problems that arose from poorly planned screening programs.

As testing became more widespread and physicians became more aware of sickle cell disease, they began to find it in white people or people who said they were white. The sickle cell gene was more widespread in other ethnic

groups than had been recognized generally by the U.S. medical community.

After several years, we began to get some resolution of the problems that had been created. In 1978, a way of diagnosing sickle cell anemia using DNA was developed. A study of the disease's natural history was instituted to identify problems it caused, and selected states began newborn screen-

ing. In 1983, the first real breakthrough supporting genetic screening for sickle cell came about when prophylactic penicillin was found to reduce mortality and morbidity in sickle cell anemic infants. This was officially accepted in 1987 by a consensus development conference at NIH. Now, newborns are the major focus of screening for sickle cell disease.

**Why Screen for Genetic Diseases?  
Pros and Cons**

Why screen for individuals at increased risk for genetic diseases who do not exhibit symptoms? On the pro or benefit side, we want to reduce morbidity and mortality. The idea is, if we could find the disease early before symptoms were present, we could avoid much pain and suffering by modifying the course of the disease through treatment and changes in lifestyle; we could increase the life span and perhaps provide a better quality of life. Unfortunately, this is true for only a minority of conditions.

Screening would, however, identify members of a high-risk population, and we could focus our attention on them. Testing for what we call susceptibility genes still may not allow us to diagnose the disease, but we could concentrate on the high-risk population for long-term follow-up and monitoring. Susceptibility screening would be much more cost-effective than expensive screening carried out on the entire population.

We also may be able to identify family members who are at increased risk. Some researchers have suggested legislation to make family testing

mandatory. They think genes do not belong to individuals; rather, genes are shared with family members who should have access to all genetic information. This was the rationale used in Washington, D.C., to justify mandatory screening for sickle cell disease. The condition was classified as a communicable disease, believe it or not—communicable from parents to children.

On the negative side of testing, many who test positive for a particular genetic marker do not get the disease even with an 80% risk, meaning that one of five persons in the high-risk group will

***Free Poster Shows Disorders,  
Traits Mapped to Chromosomes***

The revised and updated "Human Genome Landmarks: Selected Traits and Disorders Mapped to Chromosomes" is a colorful wall poster prepared by the U.S. Department of Energy Human Genome Program, with printing and mailing costs supported by QIAGEN. Informative sidebars explain genetic terms and provide URLs for finding more detailed information on the Web.

Free copies can be ordered on the poster's Web site at [www.ornl.gov/hgmis/posters/chromosome/](http://www.ornl.gov/hgmis/posters/chromosome/).



not get it. In attempting to avoid breast cancer, some women are having bilateral prophylactic mastectomies or lifelong chemotherapy. Others are having total colectomies after testing for the multiple polypsis gene—all to avoid getting a disease for which they supposedly are at risk.

Furthermore, those who will not get the disease in spite of being in a high-risk group may suffer needless emotional pain and guilt, clinical depression, and other kinds of behavioral and emotional problems that can be almost as debilitating as the disease itself. An individual identified as having the marker may be stigmatized, raising questions of employability and insurability.

And finally, family members who do not even have the marker may be stigmatized. Insurance companies may ask if anybody in their family has a series of genetically determined diseases. These companies do not have to test people to assess their risk; they need only know that somebody in the family has a certain gene.

### Lessons Learned

What can we learn from this debacle? Perhaps the most obvious lesson is not to rush into screening without first educating doctors, patients, lawmakers, and the general public. The early

screening programs also were criticized for a lack of sensitivity to issues of race, controversy surrounding the accuracy and validity of the early tests, and inadequate protection of patients' rights.

Other lessons may not be so obvious. The Institute of Medicine's

**Early screening programs were criticized for a lack of sensitivity to issues of race, controversy surrounding the accuracy and validity of the early tests, and inadequate protection of patients' rights.**

Committee on Assessing Genetic Risks, of which I was a member, prepared the book, *Assessing Genetic Risks: Implications for Health and Social Policy* (National Academy Press, 1994), on social and legal issues in genetic testing. After much discussion, a debate, and the testimony of ethicists, the committee listed certain considerations that warranted special attention.

Also in the mid-1990s, the human genome programs of NIH and the U.S. Department of Energy appointed a task force to study genetic testing in the United States. This group was charged with making recommendations to ensure the development of safe and effective genetic tests, their delivery in laboratories of assured quality, and their appropriate use by healthcare providers and consumers. In formulating recommendations, the task force reviewed three instances of genetic screening in disease diagnosis during the past quarter-century in the United States: sickle cell and Tay-Sachs in the early 1970s and neural tube defects and Down syndrome in the 1980s. The final report of the task force, *Promoting Safe and Effective Genetic Testing in the United States* (1997), is on the Web ([www.nhgri.nih.gov/ELSI/TFGT\\_final](http://www.nhgri.nih.gov/ELSI/TFGT_final)).

### Testing Recommendations

Following are some guiding principles on genetic testing formulated by the task force and similar groups.

- Sensitivity to the needs of screened groups with respect to race, ethnicity, and gender is important. A screening program should be considered only if its benefits are obvious to both the professionals and the patients or community. Appropriate genetic test-



ing, education, and counseling services should be provided.

- The impact of a genetic diagnosis on the patient can be devastating. Mandatory testing should be avoided for anything except treating diseases that, if untreated, would cause serious problems.
- Patients, physicians, and genetic counselors must understand what the tests predict or diagnose to ensure that patients can make fully informed, autonomous decisions about test

results. A big issue is how to get informed consent and what constitutes true informed consent.

- Confidentiality of test results is vital, and all forms of genetic information must be considered private. Confidentiality and privacy are tied to equity and fairness in treatment.
- Consideration should be given to how test results may affect other family members, including the impact on their health or life insurance.
- Test validity and laboratory reliability

should be monitored constantly as tests are developed and used.

### **Conclusion**

Genetic screening can be beneficial, but it also can do great harm. The increasing availability of low-cost genetic tests may tempt well-meaning institutions and legislative bodies to offer screening without appropriate education and safeguards. When genetic screening is being considered, the benefits must clearly outweigh the harm.



# Societal Concerns Arising from the New Genetics

Since its inception, the Human Genome Project has dedicated funds toward studying the ethical, legal, and social issues (ELSI) surrounding the availability of the new data and capabilities. Examples of such issues follow.

- Privacy and confidentiality of genetic information. *Who owns and controls genetic information? Is genetic privacy different from medical privacy?*
- Fairness in the use of genetic information by insurers, employers, courts, schools, adoption agencies, and the military, among others. *Who should have access to personal genetic information, and how will it be used?*
- Psychological impact, stigmatization, and discrimination due to an individual's genetic differences. *How does personal genetic information affect self-identity and society's perceptions?*



- Reproductive issues including adequate and informed consent and use of genetic information in reproductive decision making. *Do healthcare personnel properly counsel parents about risks and limitations? What are the larger societal issues raised by new reproductive technologies?*



- Clinical issues including the education of doctors and other health-service providers, people identified with genetic conditions, and the general public about capabilities, limitations, and social risks; and implementation

**How do we  
 prepare health  
 professionals for the  
 new genetics?  
 How do we prepare  
 the public to make  
 informed choices?  
 How will genetic tests  
 be evaluated and  
 regulated for accuracy,  
 reliability, and  
 usefulness?**

of standards and quality-control measures. *How do we prepare health professionals for the new genetics? How do we prepare the public to make informed choices? How will genetic tests be evaluated and regulated for accuracy, reliability, and usefulness? (Currently, there is little regulation at the federal level.) How do we as a society balance current scientific limitations and social risk with long-term benefits?*

- Uncertainties associated with gene

tests for susceptibilities and complex conditions (e.g., heart disease, diabetes, and Alzheimer's disease). *Should testing be performed when no treatment is available or when interpretation is unsure? Should children be tested for susceptibility to adult-onset diseases?*

- Fairness in access to advanced genomic technologies. *Who will benefit? Will there be major worldwide inequities?*
- Conceptual and philosophical implications regarding human responsibility, free will vs genetic determinism, and concepts of health and disease. *Do our genes influence our behavior, and can we control it? What is considered acceptable diversity? Where is the line between medical treatment and enhancement?*
- Health and environmental issues concerning genetically modified (GM) foods and microbes. *Are GM foods and other products safe to humans and the environment? How will these technologies affect developing nations' dependence on the West?*
- Commercialization of products including property rights (patents, copyrights, and trade secrets) and accessibility of data and materials. *Will patenting DNA sequences limit their accessibility and development into useful products?*

# Some Current and Potential Applications of Genome Research

## Molecular Medicine

- Improve diagnosis of disease
- Detect genetic predispositions to disease
- Create drugs based on molecular information
- Use gene therapy and control systems as drugs
- Design "custom drugs" based on individual genetic profiles

## Microbial Genomics

- Rapidly detect and treat pathogens (disease-causing microbes) in clinical practice
- Develop new energy sources (biofuels)
- Monitor environments to detect pollutants

- Protect citizenry from biological and chemical warfare
- Clean up toxic waste safely and efficiently

## Risk Assessment

- Evaluate the health risks faced by individuals who may be exposed to radiation (including low levels in industrial areas) and to cancer-causing chemicals and toxins

## Bioarchaeology, Anthropology, Evolution, and Human Migration

- Study evolution through germline mutations in lineages
- Study migration of different population groups based on maternal

genetic inheritance

- Study mutations on the Y chromosome to trace lineage and migration of males
- Compare breakpoints in the evolution of mutations with ages of populations and historical events

## DNA Forensics (Identification)

- Identify potential suspects whose DNA may match evidence left at crime scenes
- Exonerate persons wrongly accused of crimes
- Identify crime and catastrophe victims
- Establish paternity and other family relationships
- Identify endangered and protected





species as an aid to wildlife officials (could be used for prosecuting poachers)

- Detect bacteria and other organisms that may pollute air, water, soil, and food
- Match organ donors with recipients in transplant programs
- Determine pedigree for seed or livestock breeds
- Authenticate consumables such as caviar and wine

#### **Agriculture, Livestock Breeding, and Bioprocessing**

- Grow disease-, insect-, and drought-resistant crops
- Breed healthier, more productive, disease-resistant farm animals
- Grow more nutritious produce
- Develop biopesticides
- Incorporate edible vaccines into food products
- Develop new environmental cleanup uses for plants like tobacco



## Web Sites for More Information

### Minorities and Genomics

- **Minorities and Genomics**  
[www.ornl.gov/hgmis/elsi/minorities.html](http://www.ornl.gov/hgmis/elsi/minorities.html)
- **Communities of Color & Genetic Policy Project**  
[www.sph.umich.edu/genpolicy](http://www.sph.umich.edu/genpolicy)
- **Howard University National Human Genome Center**  
*NHGC aims to bring multicultural perspectives and resources to an understanding of human genome variation and its implications for disease prevention and health promotion.*  
[www.founders.howard.edu/genome/](http://www.founders.howard.edu/genome/)

### Human Genome Diversity Project

[www.stanford.edu/group/morrinst/hgdp.html](http://www.stanford.edu/group/morrinst/hgdp.html)

### Institute on Race, Healthcare, and the Law

[www.academic.udayton.edu/health/index.htm](http://www.academic.udayton.edu/health/index.htm)

### Human Genome Project

#### Human Genome Project Information

[www.ornl.gov/hgmis](http://www.ornl.gov/hgmis)

### NIH National Human Genome Research Institute (NHGRI)

[www.nhgri.nih.gov](http://www.nhgri.nih.gov)

### Ethical, Legal, and Social Issues Associated with Genomic Data and Tools

[www.ornl.gov/hgmis/elsi/elsi.html](http://www.ornl.gov/hgmis/elsi/elsi.html)

### Genetics 101

[www.ornl.gov/hgmis/project/info.html](http://www.ornl.gov/hgmis/project/info.html)

### Publications on the Initial Analysis of the Human Genome Draft Sequence

[www.ornl.gov/hgmis/project/journals/journals.html](http://www.ornl.gov/hgmis/project/journals/journals.html)

## Medicine and the Genome: CD-ROMs Available

The U.S. Department of Energy's Human Genome Program has partially funded the development of two new groundbreaking CD-ROMs that use innovative multimedia and easy navigation techniques to make the genomic revolution understandable and accessible to many audiences.

The New Genetics: Courseware for Physicians is designed for medical doctors who wish to update their knowledge about genetics and genomics. CME credit is available from Stanford University.

The New Genetics: Medicine and the Human Genome presents the same content, without CME credits, for medical students, genetic researchers, nurses, policymakers, attorneys, and others who are interested in the impact of genetics and genomics on healthcare and society.

Both CD-ROMs can be ordered through the Twisted Ladder Media Web site ([www.twistedlad-](http://www.twistedlad-)

[www.twistedladdermedia.com](http://www.twistedladdermedia.com)), which contains sample text, table of contents, feature demonstrations, and animations. The CD-ROMs were produced by Sara Tobin (Stanford University) and Ann Boughton (Twisted Ladder Media).





- **Genomes to Life** (A look at post-HGP research)  
<http://DOEGenomesToLife.org>

## **Medicine and the New Genetics**

- **Medicine and the New Genetics**  
[www.ornl.gov/hgmis/medicine/medicine.html](http://www.ornl.gov/hgmis/medicine/medicine.html)
- **NIH NHGRI Genetics Residency Training Programs**  
[www.nhgri.nih.gov/Intramural\\_research/Medical\\_genetics/Residency\\_Program/](http://www.nhgri.nih.gov/Intramural_research/Medical_genetics/Residency_Program/)
- **Gene Testing**  
[www.ornl.gov/hgmis/medicine/genetest.html](http://www.ornl.gov/hgmis/medicine/genetest.html)
- **Gene Therapy**  
[www.ornl.gov/hgmis/medicine/genetherapy.html](http://www.ornl.gov/hgmis/medicine/genetherapy.html)
- **Pharmacogenomics**  
[www.ornl.gov/hgmis/medicine/pharma.html](http://www.ornl.gov/hgmis/medicine/pharma.html)
- **Genetic Counseling**  
[www.ornl.gov/hgmis/medicine/genecounseling.html](http://www.ornl.gov/hgmis/medicine/genecounseling.html)
- **Genetic Disease Information**  
[www.ornl.gov/hgmis/medicine/assist.html](http://www.ornl.gov/hgmis/medicine/assist.html)

- **Single Nucleotide Polymorphisms (SNPs)**  
[www.ornl.gov/hgmis/faq/snps.html](http://www.ornl.gov/hgmis/faq/snps.html)

- **Genome Landmarks Selected Traits and Disorders**  
[www.ornl.gov/hgmis/posters/chromosome/](http://www.ornl.gov/hgmis/posters/chromosome/)

- **NIH NHGRI Genetic and Rare Diseases Information Center**  
[www.nhgri.nih.gov/info\\_center/](http://www.nhgri.nih.gov/info_center/)

## **Gene Testing**

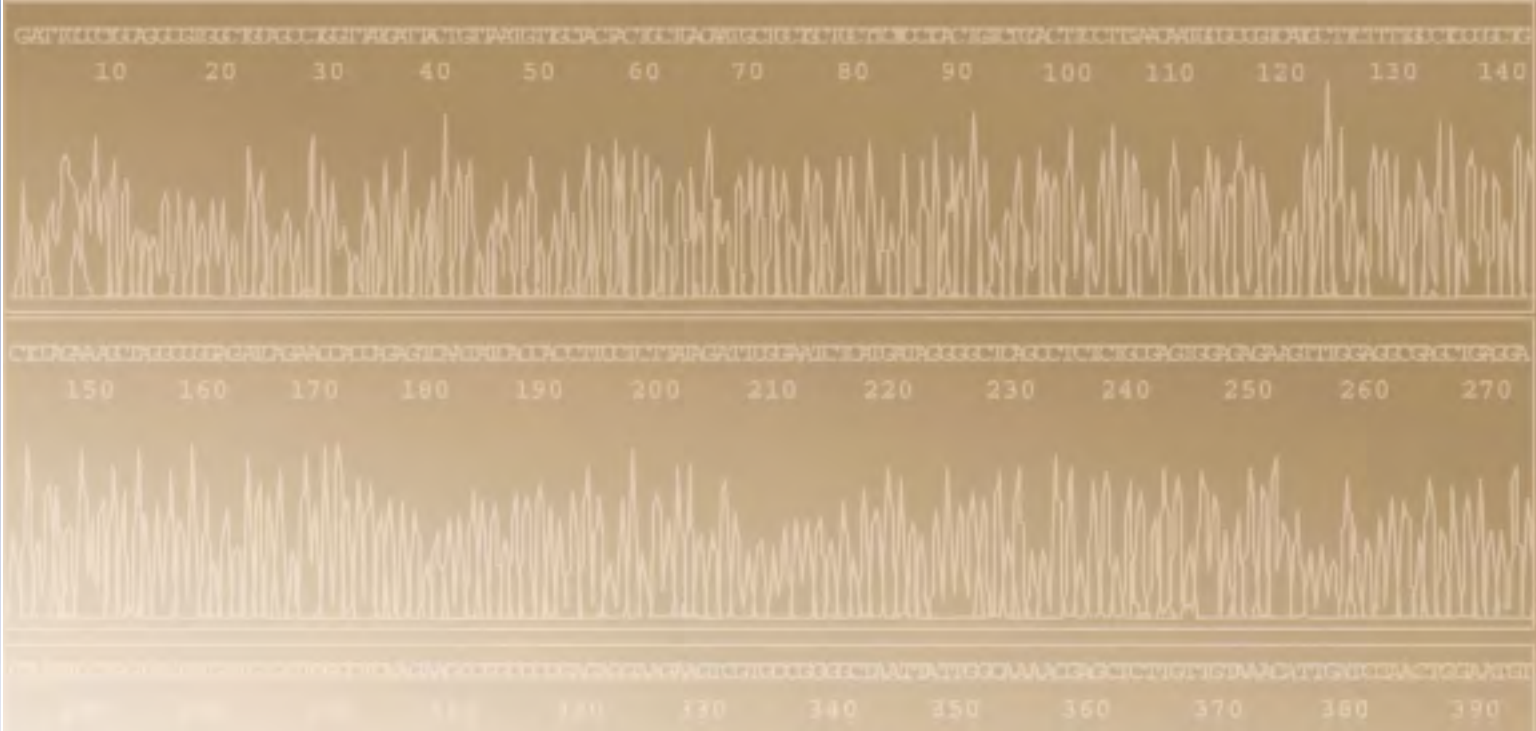
- **Secretary's Advisory Committee on Genetic Testing**  
[www4.od.nih.gov/oba/sacgt/reports/Public\\_Consultation\\_document.htm](http://www4.od.nih.gov/oba/sacgt/reports/Public_Consultation_document.htm)
- **Gene Tests/Gene Clinics**  
[www.genetests.org/](http://www.genetests.org/)
- **Online Mendelian Inheritance in Man**  
[www.ncbi.nlm.nih.gov/Omim/](http://www.ncbi.nlm.nih.gov/Omim/)

- **American Society for Human Genetics Policy Statements**  
[www.faseb.org/genetics/ashg/policy/pol-00.htm](http://www.faseb.org/genetics/ashg/policy/pol-00.htm)

## **Publications and Conference Proceedings**

- **Challenges of Genome Research for Minority Communities**  
[www.ornl.gov/hgmis/publicat/zetaphibeta/](http://www.ornl.gov/hgmis/publicat/zetaphibeta/)
- **Genome Horizons: Public Deliberations and Policy Pathways**  
[www.sph.umich.edu/genome/initial/conferenceproceedings/](http://www.sph.umich.edu/genome/initial/conferenceproceedings/)
- **National Dialogue on Genetics and Minority Issues**  
[www.karger.ch/journals/cmgl/cmgl3.htm](http://www.karger.ch/journals/cmgl/cmgl3.htm)
- **Ethical Challenges As We Approach the End of the HGP**  
[www.biol.tsukuba.ac.jp/~macer/chgp.html](http://www.biol.tsukuba.ac.jp/~macer/chgp.html)
- **Evaluating Human Genetic Diversity**  
[www.nap.edu/books/0309059313/html/](http://www.nap.edu/books/0309059313/html/)

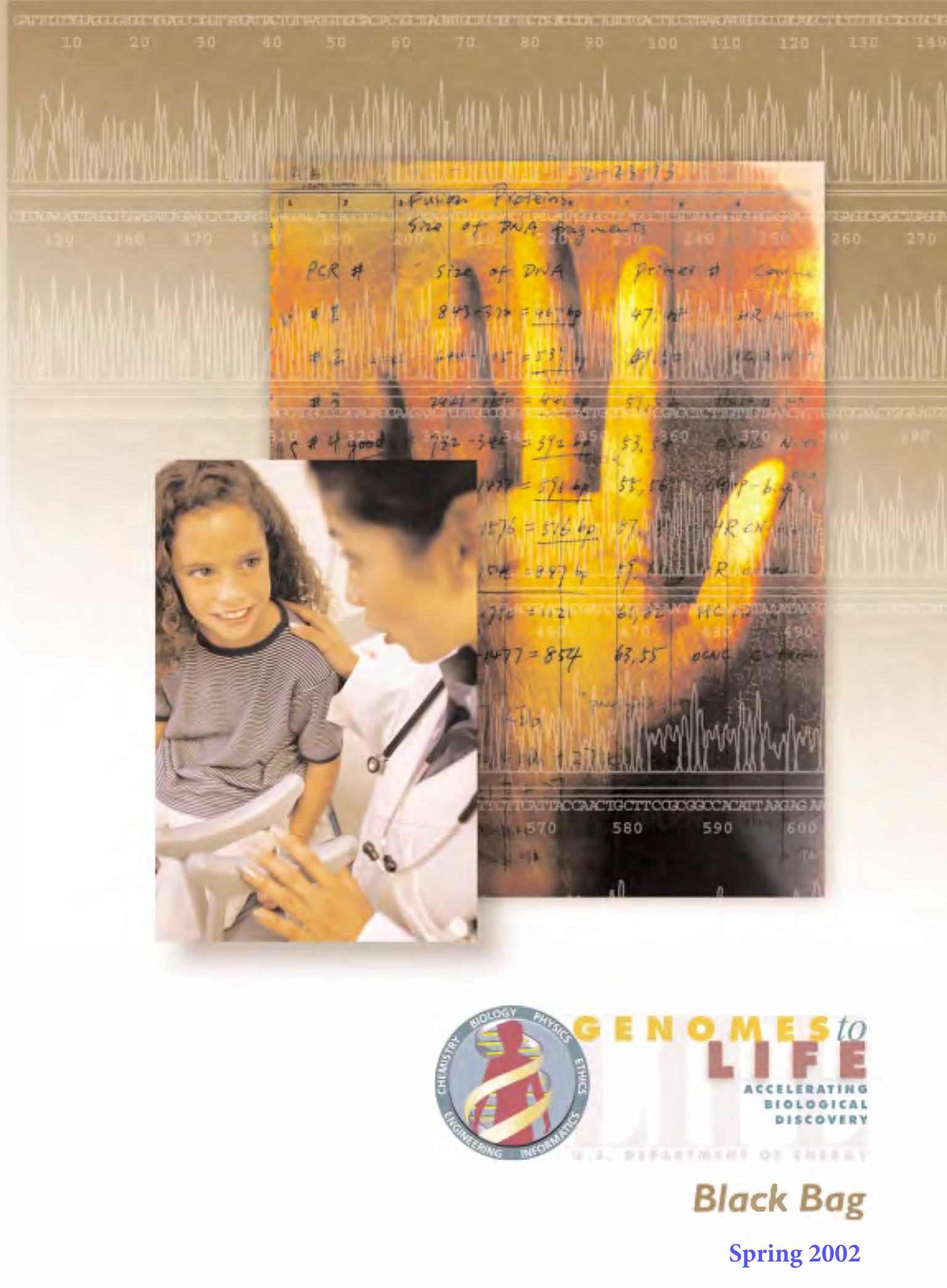
Prepared by the Human Genome Management Information System at Oak Ridge National Laboratory under the sponsorship of the DOE Human Genome Program. Contact Marissa Mills, [millsmd@ornl.gov](mailto:millsmd@ornl.gov), 865/576-6669, <http://www.ornl.gov/hgmis>.



**GENOMES** *to*  
**LIFE**  
ACCELERATING  
BIOLOGICAL  
DISCOVERY

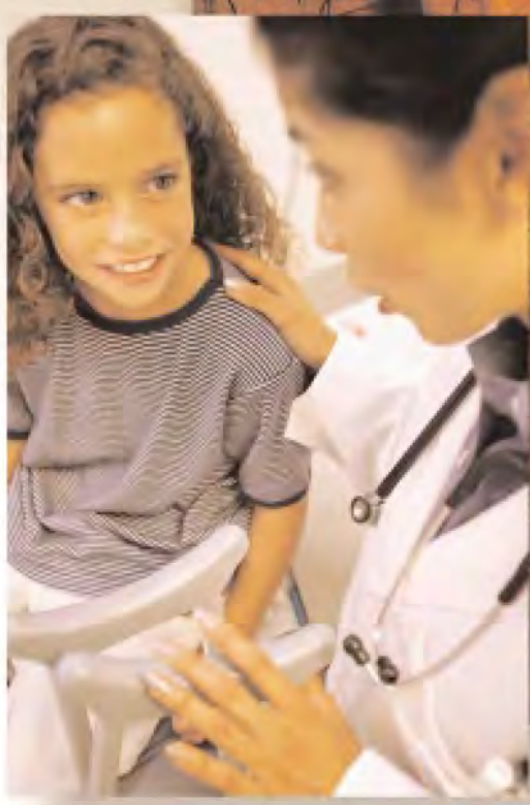
U.S. DEPARTMENT OF ENERGY

**Black Bag**



2-23-05

PCR #	Size of DNA	Primer #	Contig
# 1	843-372 = 471 bp	47, 48	HR 4-10
# 2	244-15 = 229 bp	49, 50	12, 3 W-1
# 3	2441-1254 = 1187 bp	51, 52	16, 4 W-1
# 4 good	752-345 = 407 bp	53, 54	OCNC N-1
	1477 = 591 bp	55, 56	OCNP-b-1
	1576 = 516 bp	57, 58	HR CN-1
	1042 = 887 bp	59, 60	HR CN-1
	1710 = 1121 bp	61, 62	HC 12
	1477 = 854 bp	63, 65	OCNC C-1



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