The Human Genome Program was conceived in 1986 as an initiative within the DOE Office of Health and Environmental Research, which has been renamed Office of Biological and Environmental Research (OBER) (see chart below). The program is administered primarily through the OBER Health Effects and Life Sciences Research Division (HELSRD), both directed by David A. Smith until his retirement in January 1996. Marvin Frazier is now Director of HELSRD, and OBER is led by Associate Director Aristides Patrinos, who also serves as Human Genome Program manager. Previous directors and managers are listed in the table below. OBER is within the Office of Energy Research, directed by Martha Krebs.

DOE OBER Mission

Based on mandates from Congress, DOE OBER’s principal missions are to (1) develop the knowledge necessary to identify, understand, and anticipate long-term health and environmental consequences of energy use and development and (2) employ DOE’s unique scientific and technological capabilities in solving major scientific problems in medicine, biology, and the environment. Genome integrity and radiation biology have been a long-term concern of OBER at DOE and its predecessors—the Atomic Energy Commission (AEC) and the Energy Research and Development Administration (ERDA). In the United States, the first federal support

Institutions Conducting DOE-Sponsored Genome Research

<table>
<thead>
<tr>
<th>Institutions Conducting DOE-Sponsored Genome Research</th>
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<tr>
<td>DOE national laboratories</td>
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<tr>
<td>Academic institutions</td>
</tr>
<tr>
<td>Private-sector institutions</td>
</tr>
<tr>
<td>Companies, including Small</td>
</tr>
<tr>
<td>Business Innovation Research</td>
</tr>
<tr>
<td>Foreign institutions (Russia, Canada, Israel)</td>
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</table>
for genetic research was through AEC. In the early days of nuclear energy development, the focus was on radiation effects and broadened later under ERDA and DOE to include health implications of all energy technologies and their by-products.

Today, extensive OBER-sponsored research programs on genomic structure, maintenance, damage, and repair continue at the national laboratories and universities. These and other OBER efforts support a DOE shift toward a preventive approach to health, environment, and safety concerns. World-class scientists in top facilities working on leading-edge problems spawn the knowledge to revolutionize the technology, drive the future, and add value to the U.S. economy. Major OBER research includes characterization of DNA repair genes and improvement of methodologies and resources for quantifying and characterizing genetic polymorphisms and their relationship to genetic susceptibilities.

To carry out its national research and development obligations, OBER conducts the following activities:

- Sponsors peer-reviewed research and development projects at universities, in the private sector, and at DOE national laboratories (see box, p. 59).
- Considers novel, beneficial initiatives with input from the scientific community and governmental sectors.
- Provides expertise to various governmental working groups.
- Supports the capabilities of multi-disciplinary DOE national laboratories and their unique user facilities for the nation’s benefit (p. 61).

Human Genome Program resources and technologies are focused on sequencing the human genome and related informatics and supportive infrastructure (see chart and tables, p. 62). The genomes of selected microorganisms are analyzed under the separate Microbial Genome Program.
Major DOE User Facilities and Resources Relevant to Molecular Biology Research

Although the genome program is contributing fundamental information about the structure of chromosomes and genes, other types of knowledge are required to understand how genes and their products function. Three-dimensional protein structure studies are still essential because structure cannot be predicted fully from its encoded DNA sequence.

To enhance these and other studies, DOE builds and maintains structural biology user facilities that enable scientists to gain an understanding of relationships between biological structures and their functions, study disease processes, develop new pharmaceuticals, and conduct basic research in molecular biology and environmental processes. These resources are used heavily by both academic and private-sector scientists.

Other important resources available to the research community include the clone libraries developed in the National Laboratory Gene Library Project and distributed worldwide, the GRAIL Online Sequence Interpretation Service, and the Mouse Genetics Research Facility.
Human Genome Program

Coordination and Resources

Program coordination is the responsibility of the Human Genome Task Group (see box, p. 60), which, beginning in 1997, includes Elbert Branscomb, the Joint Genome Institute’s Scientific Director. The task group is aided by the Biotechnology Consortium (which succeeded the former Human Genome Coordination Committee; see box, p. 60) to foster information exchange and dissemination. The task group administers the DOE Human Genome Program and its evolving needs and reports to the Associate Director for Biological and Environmental Research (currently Aristides Patrinos). The task group arranges periodic workshops and coordinates site reviews for genome centers, the Joint Genome Institute, databases, and other large projects. It also coordinates peer review of research proposals, administration of awards, and collaboration with all concerned agencies and organizations.

The Biotechnology Consortium provides the OBER Associate Director with external expertise in all aspects of genomics and informatics and a mechanism by which OBER can keep track of the latest developments in the field. It facilitates development and dissemination of novel genome technologies throughout the DOE system, ensures appropriate management and sharing of data and resources by all DOE contractors and grantees, and promotes interactions with other national and international genomic entities.

### Operating Expenditures and FY 1998 Projected Budget for the DOE Human Genome Program

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Operating</th>
<th>Capital Equipment</th>
<th>Construction</th>
<th>Total</th>
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</thead>
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<td>1996</td>
<td>68.3</td>
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<td>5.7</td>
<td>79.6</td>
</tr>
<tr>
<td>1997</td>
<td>73.9</td>
<td>6.0</td>
<td>1.0</td>
<td>80.9</td>
</tr>
<tr>
<td>1998*</td>
<td>79.9</td>
<td>5.2</td>
<td>0.0</td>
<td>85.1</td>
</tr>
</tbody>
</table>

*Projected expenses.

### Human Genome Program Fiscal Year Expenditures ($M)

<table>
<thead>
<tr>
<th>Year</th>
<th>Operating</th>
<th>Capital Equipment</th>
<th>Construction</th>
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<td>5.2</td>
<td>0.0</td>
<td>85.1</td>
</tr>
</tbody>
</table>

*Includes DOE laboratories’ nonresearch costs but not U.S. government administration or SBIR.

**DOE contribution to the international Human Frontiers Neurosciences Program.
Communication

The DOE Human Genome Program communicates information in a variety of ways. These communication systems include the Human Genome Management Information System (HGMIS), projects in the Ethical, Legal, and Social Issues (ELSI) Program, electronic resources, meetings, and fellowships. Some of these mechanisms are described below. For more details, see Research Highlights, ELSI projects, p. 18.

HGMIS

HGMIS provides technical communication and information services for the DOE OBER Human Genome Program Task Group. HGMIS is charged with (1) helping to communicate genome-related matters and research to contractors, grantees, other (nongenome project) researchers, and other multipliers of information pertaining to genetic research; (2) serving as a clearinghouse for inquiries about the U.S. genome project; and (3) reducing research duplication by providing a forum for interdisciplinary information exchange (including resources developed) among genetic investigators worldwide.

HGMIS publishes the newsletter Human Genome News, sponsored by OBER. Over 14,000 HGN subscribers include genome and basic researchers at national laboratories, universities, and other research institutions; professors and teachers; industry representatives; legal personnel; ethicists; students; genetic counselors; physicians; science writers; and other interested individuals.

HGMIS also produces the DOE Primer on Molecular Genetics; a compilation of ELSI abstracts; and reports on the DOE Human Genome and Microbial Genome Programs, contractor-grantee workshops, and other related subjects.

Electronic versions of the primer and other HGMIS publications are available via the World Wide Web. HGMIS also initiates and maintains other related Web sites (see DOE Electronic Genome Resources section below and DOE Web Sites at right).

In addition to their print and online publishing efforts, HGMIS staff members answer questions generated via Web sites, telephone, fax, and e-mail. They also furnish customized information about the genome project for multipliers of information (contact: Betty Mansfield at 423/576-6669, Fax: /574-9888, mansfieldbk@ornl.gov).

DOE Electronic Genome Resources

Web Sites. The DOE Human Genome Program Home Page displays pointers to other programs within OBER and the Office of Energy Research. Links are made to additional biological and environmental information and to HGMIS, Genome Database, and other sites.

HGMIS initiates and maintains the searchable Human Genome Project Information Web site. This site contains more than 1700 text files of information for multidisciplinary technical audiences as well as for lay persons interested in learning about the science, goals, progress, and history of the project. Users include almost all levels of students; education, medical, and legal professionals; genetic society and support group members; biotechnology and pharmaceutical industry personnel; administrators; policymakers; and the press.

The site also houses a section of frequently asked questions, a quick fact finder, Primer on Molecular Genetics, all issues of Human Genome News, DOE Human Genome Program and contractor-grantee workshop reports, To Know Ourselves, historical documents, research abstracts, calendars of genome events, and hundreds of links to genome research and educational sites. More than 1000 other Web pages link to this site, resulting in more than 100,000 text file transfers each month. This
The DOE Human Genome Program and Human Genome Project Information Web sites offer both general and scientific audiences thousands of text files and links for comprehensive coverage of all aspects of genome research worldwide. See text (pp. 63 and 65) for further details.
HGMIS site has received a Four-Star designation from the Magellan Group and the Editor’s Choice Award from LookSmart.

Genome-project and related meetings are listed at a Web site (see box, p. 63), through which users can register and submit research abstracts. Another listed related site discusses issues at the critical intersection of genetics and the court system. This Web page is part of a project to educate and prepare the judiciary for the coming onslaught of cases involving genetic issues and data.

Newsgroup. The Human Genome Program Newsgroup operates through the BIOSCI electronic bulletin board network to allow researchers worldwide to communicate, share ideas, and find solutions to problems. Genome-related information is distributed through the newsgroup, including requests for grant applications, reports from recent scientific and advisory meetings, announcements of future events, and listings of free software and services (genome-pr@net.bio.net or http://www.bio.net).

Postdoctoral Fellowships

OBER established the Human Genome Distinguished Postdoctoral Research Program in 1990 to support research on projects related to the DOE Human Genome Program. Beginning in FY 1996, the Human Genome Distinguished Postdoctoral Fellowships were merged with the Alexander Hollaender Distinguished Postdoctoral Fellowships, which provide support in all areas of OBER-sponsored research. Postdoctoral programs are administered by the Oak Ridge Institute for Science and Education, a university consortium and DOE contractor. For additional information, contact Linda Holmes (423/576-3192, holmesl@orau.gov) or see the Web site (http://www.orau.gov/ober/hollaend.htm).

Alexander Hollaender Distinguished Postdoctoral Fellows in Genome Research

1996 Cymbeline Culiat (Oak Ridge National Laboratory): Cloning of a Mouse Gene Causing Severe Deafness and Balance Defects

Tau-Mu Yi (Laboratory of Structural Biology and Molecular Medicine, Los Angeles): Structure-Function Analysis of Alpha-Factor Receptor

1997 Jeffrey Koshi (Los Alamos National Laboratory): Construction, Analysis, and Use of Optimal DNA Mutation Matrices

Sandra McCutchen-Maloney (Lawrence Livermore National Laboratory): Structure and Function of a Damage-Specific Endonuclease Complex

Human Genome Distinguished Postdoctoral Fellows

Names of past and current fellows in genome topics are given below with their research institutions and titles of proposed research. For 1996 research abstracts, refer to Index of Principal and Coinvestigators on p. 71 in Part 2 of this report.

1994

Mark Graves (Baylor College of Medicine): Graph Data Models for Genome Mapping

William Hawe (Duke University): Synthesis of Peptide Nucleic Acids for DNA Sequencing by Hybridization

Jingyue Ju (University of California, Berkeley): Design, Synthesis, and Use of Oligonucleotide Primers Labeled with Energy Transfer–Coupled Dyes

Mark Shannon (Oak Ridge National Laboratory): Comparative Study of a Conserved Zinc Finger Gene Region

1995

Evan Eichler (Lawrence Livermore National Laboratory): Identification, Organization, and Characterization of Zinc Finger Genes in a 2-Mb Cluster on 19p12

Kelly Ann Frazer (Lawrence Berkeley National Laboratory): In Vivo Complementation of the Murine Mutations Grizzled, Mocha, and Jitteri

Soo-in Hwang (Lawrence Berkeley National Laboratory): Positional Cloning of Oncogenes on 20q13.2

James Labrenz (University of Washington, Seattle): Error Analysis of Principal Sequencing Data and Its Role in Process Optimization for Genome-Scale Sequencing Projects

Marie Ruiz-Martinez (Northeastern University): Multiplex Purification Schemes for DNA Sequencing–Reaction Products: Application to Gel-Filled Capillary Electrophoresis

Todd Smith (University of Washington, Seattle): Managing the Flow of Large-Scale DNA Sequence Information

1996

Cymbeline Culiat (Oak Ridge National Laboratory): Cloning of a Mouse Gene Causing Severe Deafness and Balance Defects

1997

Jeffrey Koshi (Los Alamos National Laboratory): Construction, Analysis, and Use of Optimal DNA Mutation Matrices

Sandra McCutchen-Maloney (Lawrence Livermore National Laboratory): Structure and Function of a Damage-Specific Endonuclease Complex
The laser-based flow cytometer developed at DOE national laboratories enables researchers to separate human chromosomes for analysis.
[Source: Los Alamos National Laboratory]
The U.S. Human Genome Project is supported jointly by the Department of Energy (DOE) and the National Institutes of Health (NIH), each of which emphasizes different facets. The two agencies coordinate their efforts through development of common project goals and joint support of some programs addressing ethical, legal, and social issues (ELSI) arising from new genome tools, technology, and data.

Extraordinary advances in genome research are due to contributions by many investigators in this country and abroad. In the United States, such research (including nonhuman) also is funded by other federal agencies and private foundations and groups. Many countries are major contributors to the project through international collaborations and their own focused programs. Coordinating and facilitating these diverse research efforts around the world is the aim of the nongovernmental international Human Genome Organisation.

Some details of U.S. and worldwide coordination are provided below.

**U.S. Human Genome Project: DOE and NIH**

In 1988 DOE and NIH developed a Memorandum of Understanding that formalized the coordination of their efforts to decipher the human genome and thus “enhance the human genome research capabilities of both agencies.” In early 1990 they presented Congress with a joint plan, *Understanding Our Genetic Inheritance, The U.S. Human Genome Project: The First Five Years (1991–1995)*. Referred to as the Five-Year Plan, it contained short-term scientific goals for the coordinated, multiyear research project and a comprehensive spending plan. Unexpectedly rapid progress in mapping prompted early revision of the original 5-year goals in the fall of 1993 [Science 262, 43–46 (October 1, 1993)]. Current goals, which run through September 30, 1998, are listed on page 5; text of both 5-year plans is accessible via the Web (http://www.ornl.gov/hgmis/project/hgp.html).

DOE and NIH have adopted a joint policy to promote sharing of genome data and resources for facilitating progress and reducing duplicated work. (See Appendix B: DOE-NIH Sharing Guidelines, p. 75.)

**ELSI Considerations**

NIH and DOE devote at least 3% of their respective genome program budgets to identifying, analyzing, and addressing the ELSI considerations surrounding genome technology and the data it produces. The DOE ELSI component focuses on research into the privacy and confidentiality of personal genetic information, genetics relevant to the workplace, commercialization (including patenting) of genome research data, and genetic education for the general public and targeted communities. The NIH ELSI component supports studies on a range of ethical issues surrounding the conduct of genetic research and responsible clinical integration of new genetic technologies, especially in testing for mutations associated with cystic fibrosis and heritable breast, ovarian, and colon cancers.

In 1990, the DOE-NIH Joint ELSI Working Group was established to identify, address, and develop policy options; stimulate bioethics research; promote education of professional and lay groups; and collaborate with such international groups as the Human Genome Organisation (HUGO); United Nations Educational, Scientific, and Cultural Organization; and the European Community. Research funded by the U.S. Human Genome Project through the joint working group has produced policy recommendations in various areas. In May 1993, for
example, the DOE-NIH Joint ELSI Working Group Task Force on Genetic Information and Insurance issued a report with recommendations for managing the impact of advances in human genetics on the current system of healthcare coverage. In 1996, the working group released guidelines for investigators on using DNA from human subjects for large-scale sequencing projects. The guidance emphasizes numerous ways to preserve donor anonymity [see Appendix C, p. 77, and the World Wide Web (http://www.ornl.gov/hgmis/archive/nchgrdoe.html)].

In 1997, following an evaluation, the two agencies modified the ELSI working group into the ELSI Research and Program Evaluation Group (ERPEG). ERPEG will focus more specifically on research activities supported by DOE and NIH ELSI programs.

**Other U.S. Programs**

The potential impact of genome research on society and the rapid growth of the biotechnology industry have spurred the initiation of other genome research projects in this country and worldwide. These projects aim to create maps of the human genome and the genomes of model organisms and several economically important microbes, plants, and animals.

- The DOE Microbial Genome Program, begun in 1994, is producing complete genome sequence data on industrially important microorganisms, including those that live under extreme environmental conditions. The sequences of several microbial genomes have been completed. [http://www.er.doe.gov/production/ober/EPR/mig_top.html]

- In 1990, the National Science Foundation, DOE, and the U.S. Department of Agriculture (USDA) initiated a project to map and sequence the genome of the model plant *Arabidopsis thaliana*. The goal of this project is to enhance fundamental understanding of plant processes. In 1996, the three agencies began funding systematic, large-scale genomic sequencing of the 120-megabase *Arabidopsis* genome, with the goal of completing it by 2004, with DOE support through the Office of Basic Energy Sciences. [http://pgec-genome.pw.usda.gov/agi.html]

- USDA also funds animal genome research projects designed to obtain genome maps for economically important species (e.g., corn, soybeans, poultry, cattle, swine, and sheep) to enable genetic modifications that will increase resistance to diseases and pests, improve nutrient value, and increase productivity.

- The Advanced Technology Program (ATP) of the U.S. National Institute of Standards and Technology promotes industry-government partnerships in DNA sequencing and biotechnology through the Tools for DNA Diagnostics component. DOE staff participates in the ATP review process (see box, p. 22). [http://www.atp.nist.gov]

- In 1997 the NIH National Cancer Institute established the Cancer Genome Anatomy Project (CGAP) to develop new diagnostic tools for understanding molecular changes that underlie all cancers (http://www.ncbi.nlm.nih.gov/ncicgap). DOE researchers are generating clone libraries to support this effort.

**International Collaborations**

The current DOE-NIH Five-Year Plan commends the “spirit of international cooperation and sharing” that has characterized the Human Genome Project and played a major role in its success. Cooperation includes collaborations among laboratories in the United States
and abroad as well as extensive sharing of materials and information among genome researchers around the world. The DOE Human Genome Program supports many international collaborations as well as grantees in several foreign institutions.

Collaborations involving the DOE human genome centers include mapping chromosomes 16 and 19, developing resources, and constructing the human gene map from shared cDNA libraries. These libraries were generated by the Integrated Molecular Analysis of Gene Expression (called IMAGE) Consortium initiated by groups at Lawrence Livermore National Laboratory, Columbia University, NIH National Institute of Mental Health, and Généthon (France).

Investigators from almost every major sequencing center in the world met in Bermuda in February 1996 and again in 1997 to discuss issues related to large-scale sequencing. These meetings were designed to help researchers coordinate, compare, and evaluate human genome mapping and sequencing strategies; consider new sequencing and informatics technologies; and discuss release of data.

**Human Genome Organisation**

Founded by scientists in 1989, HUGO is a nongovernmental international organization providing coordination functions for worldwide genome efforts. HUGO activities range from support of data collation for constructing genome maps to organizing workshops. HUGO also fosters exchange of data and biomaterials, encourages technology sharing, and serves as a coordinating agency for building relationships among various government funding agencies and the genome community.

HUGO offers short-term (2- to 10-week) travel awards up to $1500 for investigators under age 40 to visit another country to learn new methods or techniques and to facilitate collaborative research between the laboratories.

HUGO has worked closely with international funding agencies to sponsor single-chromosome workshops (SCWs) and other genome meetings. Due to the success of these workshops as well as the shift in emphasis from mapping to sequencing, DOE and NIH began to phase out their funding for international SCWs in FY 1996 but encouraged applications for individual SCWs as needed. In 1996, HUGO partially funded an international strategy meeting in Bermuda on large-scale sequencing. Principles regarding data release and a resources list developed at the meeting are available on the HUGO Web site (http://hugo.gdb.org/hugo.html).

Membership in HUGO (over 1000 people in more than 50 countries) is extended to persons concerned with human genome research and related scientific subjects. Its current president is Grant R. Sutherland (Adelaide Women and Children’s Hospital, Australia). Directed by an 18-member international council, HUGO is supported by grants from the Howard Hughes Medical Institute and The Wellcome Trust.
Los Alamos National Laboratory researchers Peter Goodwin and Rhett Affleck load a sample of fluorescently labeled DNA into an ultrasensitive flow cytometer used to detect single cleaved nucleotides. [Source: Lynn Clark, LANL]