BIOLOGY PHYSICS MATHEMATICS ENGINEERING CHEMISTRY

# Human Genome quarterly

*A Forum for Human Genome Information Exchange*

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## DOE Human Genome Program

The Human Genome Initiative was proposed by the U.S. Department of Energy in 1986 following the completion of a human genome project feasibility workshop in Santa Fe, New Mexico. In April 1987 the initiative was endorsed by a report from the Department's Health and Environmental Research Advisory Committee (HERAC). The HERAC report urged DOE and the nation to commit to a large, long-term, multidisciplinary, technological undertaking to order and sequence the human genome.

Involvement in this initiative was seen as a consequence of DOE's demonstrated expertise in handling projects of this size and scope, and of the commitment of the Office of Health and Environmental Research (OHER) to evaluating the health effects of energy-related agents and to utilizing DOE resources for beneficial applications in biology and medicine. A basic understanding of the effects of damage to the genome was seen as a vital contribution to this mission.

Subsequent reports from the National Academy of Sciences and the Congressional Office of Technology Assessment supported the HERAC report by endorsing a major national effort at a sustained level of $200 million annually. The initiative was seen as having substantive long-term impacts on basic science and the biotechnology and pharmaceutical industries, as well as on the practice of medicine.

The long-range goal of this dedicated research is to develop and provide the broad array of resources and technologies that will allow the complete characterization of the human genome at the molecular level.

The near-term objectives of the initiative, which received program status in 1987, are to:

- produce libraries of linearly ordered DNA fragments specific for each human chromosome,
- improve significantly the efficiency of sequencing DNA, and
- upgrade the computer capabilities needed to organize, disseminate, and interpret the sequence of the human genome.

Research and development in each of these areas is progressing in DOE national laboratories, universities, and the private sector at an FY89 support level of $17.5 million (Fig. 1).

The ordered chromosome-specific DNA fragments currently being produced will

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## Editor's Notes

As a representative of the Human Genome Management Information System, sponsored by the Department of Energy (DOE) at Oak Ridge National Laboratory, we would like to welcome you to our first publication of the *Human Genome Quarterly*. Our role in the Human Genome Program is:

- to assist the Office of Health and Environmental Research in achieving its mission of communicating issues relevant to human genome research to the public and
- to provide a forum for exchange of information to all individuals and agencies involved in genome research.

To fulfill these goals, we will be producing technical reports (topics to be selected by DOE), the *Human Genome Quarterly*, and an electronic bulletin board, which is currently on-line. It will be available to interested persons later this year and will feature:

- news and comments from DOE/OHER,
- summaries/highlights of research projects,
- meeting announcements/calendar,
- literature highlights,
- Human Genome Program contacts,
- international activities, and
- suggestions/comments from users.

In this first issue of the *Human Genome Quarterly*, our goal was to give the reader an overview of DOE's role and organization with respect to the Human Genome Program.

We invite and welcome suggestions as to content and format as well as contributions for publication. We will make every attempt to address the issues brought forward by our readers. Please direct correspondence to our address at Oak Ridge National Laboratory. ◇

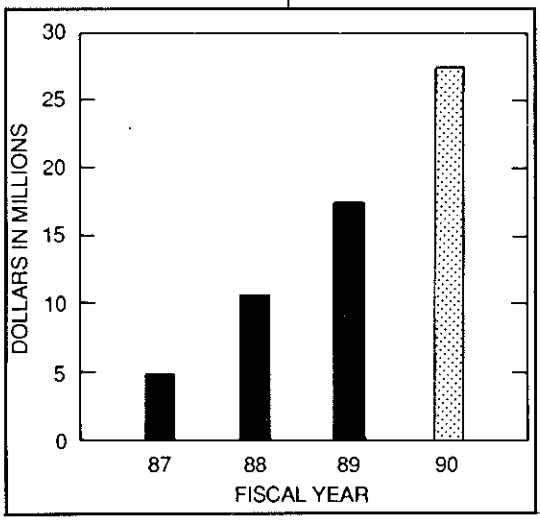
**Genome Program** *(from page 1)*

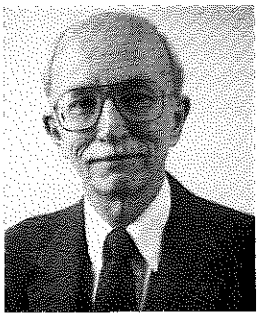
someday be decoded into a reference human genome sequence of 3.5 billion base pair subunits. Such sequence information will greatly advance our understanding of gene function, especially in the area of genetic diseases and as a basis for determining individual sensitivity to radiation and environmental chemicals. However, the inclusion of an intensive sequencing effort in this program must await a significant improvement in the cost effectiveness of DNA sequencing technologies.

The two most active federal agencies in this area of research, the National Institutes of Health (NIH) and DOE, have signed a Memorandum of Understanding to facilitate cooperation and coordination of genome research and development and to establish a joint advisory committee to coordinate these activities. The memorandum also establishes an interagency working group in which staff members of NIH and DOE meet regularly to discuss research of mutual interest, as well as agency priorities. In October 1988, DOE established a Human Genome Steering Committee, composed of key DOE-supported scientists, to help coordinate the Department's multidisciplinary genome research and development activities. ◇

*Submitted by Dr. Benjamin J. Barnhart*
*DOE Human Genome Program Manager*

**Fig. 1. DOE Support for Human Genome Research.**



**Dr. Benjamin J. Barnhart**

### Barnhart To Head Human Genome Program

Dr. Benjamin J. Barnhart was appointed Program Manager of the Human Genome Program for the Office of Health and Environmental Research (OHER) of the U.S. Department of Energy (DOE) in January 1989. He is the principal point of contact in OHER for this rapidly growing multidisciplinary program. His responsibilities also include management of research projects which address the genetic effects of ionizing radiations and their mechanisms of action at the cellular and molecular levels. He has been with the DOE since 1984.

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# DOE Human Genome Steering Committee Announced

The Human Genome Steering Committee (HGSC), established in October of 1988, is part of the management structure of the Department of Energy (DOE) Human Genome Program. Members of the committee are:

- Dr. Charles R. Cantor, Director of the Human Genome Center at Lawrence Berkeley Laboratory (LBL);
- Dr. George I. Bell, Acting Director of the Center for Human Genome Studies, Los Alamos National Laboratory (LANL);
- Dr. Anthony V. Carrano, Director of the Lawrence Livermore National Laboratory (LLNL) Human Genome Project; and

representing the grantees:

- Dr. C. Thomas Caskey, Baylor College of Medicine and
- Dr. Leroy Hood, California Institute of Technology.

Dr. Benjamin J. Barnhart, Human Genome Program Manager, and Dr. Gerald Goldstein, Office of Health and Environmental Research (OHER), serve as ex-officio members for DOE. The National Institutes of Health, the National Science Foundation, the Department of Agriculture, and the Howard Hughes Medical Institute each send a participating observer.

The specific tasks of the HGSC are to:

- assist OHER with coordination of DOE-funded genome research;
- facilitate the transfer of technology arising from genome research to other researchers and private industry;
- ensure availability and management of data and biological materials;
- optimize constructive overlap among research groups and encourage new joint projects;
- serve with OHER staff as representatives of DOE/OHER to other government and international committees;
- assist in communicating the scientific program to the U.S. Congress, the press, and the public; and
- inform DOE/OHER on scientific issues.

The HGSC has met twice since its founding. The first meeting was at Livermore, California, in October 1988. The second took place in San Francisco, during the January 1989 meeting of the American Association for the Advancement of Science, where each of the appointed members spoke at a symposium on the National Human Genome Project. The committee plans to meet at least four times each year in day-long, closed meetings. Reports of each meeting are available to contractors, grantees, and other interested parties.

In its first meeting, HGSC recognized the importance of communication among DOE-funded projects and stressed the need for a policy on sharing data and samples. As a result, a policy was developed and has been recommended to DOE. Briefly stated, it says that all materials and data should be shared freely within one year of characterization or publication. The committee also supports development of an interagency policy on sharing data and materials.

At the January meeting, the committee scheduled a Human Genome Program Grantee and Contractor Workshop to be held in Santa Fe, New Mexico, on November 3 and 4. At this workshop, each laboratory involved in the DOE program will present either a talk or poster on results and work in progress.

The HGSC appointed Dr. Thomas G. Marr (LANL) to serve as Chairman of the DOE Human Genome Computational Task Force (HGCTF). The first priority of this group is to design the database for physical mapping and develop automated methods of map integration and data sharing (refer to HGCTF article, page 5). ◇

*Submitted by Dr. Sylvia J. Spengler*
*Executive Officer, HGSC*
*Lawrence Berkeley Laboratory*

Topics for discussion at the April HGSC meeting will include:

- technology transfer,
- costs of sharing data and materials, and
- a workshop on Large Insert Cloning, planned for late 1989.

## Steering Committee Chairman

Dr. Charles R. Cantor

Charles R. Cantor is the Director of the Human Genome Center at Lawrence Berkeley Laboratory and Higgens Professor and Chairman of the Department of Genetics and Development at the Columbia University's College of Physicians and Surgeons. He received his A.B. from Columbia and his Ph.D. from the University of California at Berkeley.

Cantor's career has been devoted to molecular biology and molecular biophysics, particularly in nucleic acids research. His group developed the pulse-gel electrophoresis technique to separate DNA fragments. He is an internationally recognized expert in the fields of genetic mapping and sequencing. He is an Alfred P. Sloan Foundation Fellow, Gugenheim Fellow, and Fellow of the American Association for the Advancement of Science. In 1978 he was given the Eli Lilly Award in Biological Chemistry and in 1985 received an Outstanding Investigator Grant by the National Cancer Institute. He was elected to the National Academy of Sciences in 1988. ◇

## Meet the Steering Committee Members

Dr. George I. Bell

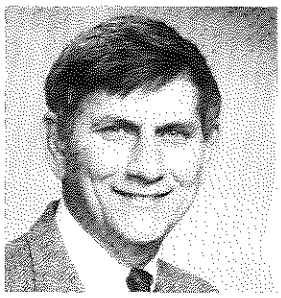
**George I. Bell** is Acting Director of the Center for Human Genome Studies at Los Alamos National Laboratory in Los Alamos, New Mexico. He received his B.S. in physics from Harvard College and a Ph.D. in theoretical physics from Cornell University.

Bell's recent research interests include supercomputing, computational challenges in mapping and sequencing the human genome, and theoretical immunology. He was awarded the David A. Sowles Medal in 1981 and is a Scholar in Human Biology of the Eleanor Roosevelt Institute for Cancer Research and Florence R. Sabin Laboratories for Developmental Medicine. Bell is a member of the New York Academy of Science and a Fellow of the American Association for the Advancement of Science, the American Physical Society, and the American Nuclear Society. ◇

Dr. Anthony V. Carrano

**Anthony V. Carrano** is the Genetics Section leader of the Biomedical Sciences Division and Director of the Livermore Human Genome Project at Lawrence Livermore National Laboratory in Livermore, California. He received his B.S. in chemistry from Rensselaer Polytechnic Institute and his Ph.D. in biophysics from the University of California at Berkeley.

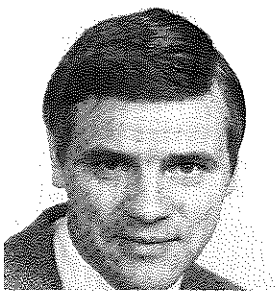
Carrano's research has centered on cytogenetics, molecular cytogenetics, mechanisms of mutagenic damage and repair, and genetic consequences of mutagen exposure. He has published methods for fluorescence-based, high-resolution, semiautomated methods for DNA fingerprinting. He is closely involved in the National Gene Library Project. He was a U.S. Atomic Energy Commission Special Fellow from 1968 to 1970 and received the Environmental Mutagen Society Recognition Award in 1986. He is a member of the Environmental Protection Agency Gene-Tox Committees on Chromosomal Aberration and Sister Chromatid Exchange. ◇



Dr. C. Thomas Caskey

**C. Thomas Caskey** is Professor and Director of the Institute for Molecular Genetics at the Baylor College of Medicine in Houston, Texas. Also at Baylor, he holds the Henry and Emma Meyer Chair in Molecular Genetics, is Chief of the Medical Genetics Section, and investigator at the Howard Hughes Medical Institute. He received his B.S. from the University of South Carolina and M.D. degree from Duke University Medical School.

Caskey's research interests include inherited disease and mammalian genetics. He has been the Josiah Macy, Jr., Faculty Scholar and is a Fellow of the American College of Physicians. His research review panel memberships include the National Advisory General Medical Sciences Council of NIH/DHHS and the U.S. Congress Office of Technology Assessment Advisory Panel on Mapping the Human Genome. ◇



Dr. Leroy Hood

**Leroy Hood** is the Ethel Wilson Bowles and Robert Bowles Professor of Biology and Director of the National Science Foundation's Science and Technology Center for Integrated Protein and Nucleic Acid Chemistry and Biological Computation at the California Institute of Technology (Cal. Tech.). Additionally, he is Director of the Cancer Center at Cal. Tech. He has an M.D. from the Johns Hopkins Medical School and a Ph.D. in biochemistry from Cal. Tech.

Hood's laboratory has played a major role in developing automated microchemical instrumentation which permits the sensitive sequence analysis of proteins and DNA and the synthesis of peptides and gene fragments. He is a member of the National Academy of Sciences and the American Association of Arts and Sciences. Among his awards are the Ricketts Medal from the University of Chicago, the 3M Life Sciences Award, the California Scientist of the Year Award, the Louis Pasteur Award for Medical Innovation, the ARCS Foundation Man of Science Award, the Isco Award, the Dickson Prize in medicine, the Albert Lasker Basic Medical Research Award, and the Shacknai Prize in Immunology and Cancer Research from Hebrew University's Hadassah Medical School. ◇

## Human Genome Computational Task Force Formed

The DOE Human Genome Steering Committee has appointed the Human Genome Computational Task Force (HGCTF). The mission of the task force is to:

1. advise the HGSC on technical matters (e.g., the feasibility, cost, and resources of computational aspects of the Human Genome Program),
2. provide a focal point for responding to the computational needs and priorities of the experimental efforts within the DOE community,
3. provide a forum for detailed discussion concerning on-going and proposed research and development activities within the DOE community,
4. develop protocols for the sharing of data over networks, and
5. provide an official interface to the private sector for negotiating DOE collaborator license agreements for commercial product pricing, use, and evaluation.

Members of the DOE Human Genome Computational Task Force are listed below:

- Dr. Thomas G. Marr, Chairman, Los Alamos National Laboratory;
- Dr. Elbert Branscom, Lawrence Livermore National Laboratory;
- Dr. Eric Lander, Whitehead Institute for Biomedical Research;
- Dr. Stanley Letovsky, Software Engineering Institute, Carnegie Mellon University;
- Dr. Eugene Myers, Department of Computer Science, University of Arizona;
- Dr. Ross Overbeek, Computer Science Laboratory, Argonne National Laboratory;
- Dr. Richard Roberts, Cold Spring Harbor Laboratory; and
- Dr. Edward Theil, Lawrence Berkeley Laboratory.

The task force is pursuing open collaboration with other groups or agencies involved in genome mapping and sequencing. ◇

*Submitted by Dr. Thomas G. Marr*

## Computer Scientists Join Molecular Biologists In Genome Workshop

Restriction mapping, crystallography, relational databases, and fifth-generation technology were among the topics discussed by an international panel of computer scientists and biologists at Argonne National Laboratory (ANL) on November 3–5, 1988.

The panel, which included experts from the United States, Europe, and Japan, addressed the question, "How can advanced computer technologies help meet the needs of researchers in biological sequencing?" The answers to this question formed the basis of a strategy document outlining how the Department of Energy might best allocate resources for the development of computational tools for biological sequencing projects.

The three-day meeting began with tutorials on genome sequencing and advanced computer technologies. Lively discussion followed the tutorials, with the panel members disagreeing on the relative merits of integrated vs heterogeneous databases.

The participants agreed unanimously, however, that a set of model projects should be established to explore all facets of the problem. Several individual tools that should be explored as part of the model projects were identified, and these include:

- rapid analysis tools that would enable users to search a database quickly,
- dynamic simulation tools for structural analysis of cells and organisms, and
- improved pattern-recognition tools that would exploit logic programming techniques to aid in protein analysis.

Copies of the 72-page report, *Proceedings of the Workshop on Advanced Computer Technologies and Biological Sequencing* (ANL-88-45), are available from Gail W. Pieper, ANL. ◇

*Submitted by Gail W. Pieper*
*Senior Technical Editor, MCS Division*
*Argonne National Laboratory*
*Building 221, Argonne, IL 60439*

Human Genome quarterly

This newsletter is intended to facilitate communication among genome researchers. Suggestions and contributions are invited.

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# Workshop Focuses on Interface Between Computational Science and Nucleic Acid Sequencing

**Molecular Biologists Regard Computer Databases and Analysis Programs as Important to Research**

**Need Seen for Image-Processing, Data-Management Systems**

Approximately 100 molecular biologists, computer scientists, mathematicians, and other scientists in diverse fields met in Santa Fe, New Mexico, on December 12–16, 1988, at a workshop on "The Interface Between Computational Science and Nucleic Acid Sequencing." Supported by the Department of Energy (DOE) Office of Health and Environmental Research (OHER), the workshop was largely motivated by the national human genome research community, which has as one of its goals the mapping of the human genome.

This activity will include the development of physical maps of each chromosome and, ultimately, may include determining the sequence of the three billion nucleotides that make up the human genome. The capture, organization, availability, and comprehension of this information will require the development and, in some cases, the invention of many computational tools. The workshop was organized to discuss:

- the computational challenges posed by this information onslaught,
- the current state of relevant databases and analysis methods, and
- directions for needed research and development.

Although the workshop topics were given special urgency by the Human Genome Program, other "megasequencing" projects to sequence bacterial and yeast genomes, together with recent progress in sequencing technology, also made the workshop timely.

The workshop participants reviewed anticipated needs of the Human Genome and other programs, together with existing capabilities. At present, the human genetic linkage map is assembled by the Howard Hughes Medical Institute Human Gene Mapping Library, while the sequence data are assembled collaboratively by three groups:

- GenBank (Los Alamos National Laboratory (LANL) and Intelligenetics, Mountain View, California),
- European Molecular Biology Laboratory (EMBL) Data Library (Heidelberg), and
- DNA Data Bank of Japan (Mishima).

**Investigators Need Easy Access to Databases**

A pilot project has been started at LANL to provide a national repository for physical mapping data of various resolutions. Workshop participants agreed that there is a need for image-processing and data-management systems that will enable individual laboratories not only to organize their own map and sequence data, but also to submit them directly to central databases. GenBank will soon appear in the form of a relational database, but some participants saw a need for object-oriented and hierarchical databases in the future. It was agreed that all databases need to be linked and easily accessible to individual investigators through their scientific workstations. The National Library of Medicine, through its Center for Biotechnology Information, and the Center for Human Genome Studies at LANL plan to play major roles in coordinating this effort.

Detection of functionally significant patterns in DNA and protein sequences was a major topic at the workshop. A standard procedure is to compare a new sequence with all known ones in a search for significant similarity. Reports were given on the use of parallel computers for such comparisons.

In addition, special-purpose computer chips are being designed for sequence comparisons (T. Hunkapiller, California Institute of Technology). Some exciting results were reported by A. Lapedes (LANL) in the use of adaptive networks to detect protein coding regions, including the intron-exon splice junctions, in human DNA. Sequences with the potential to regulate gene expressions are more difficult to detect. Many of these are sequences that are recognized by specific proteins, and C. Benham (Mt. Sinai School of Medicine) gave an elegant review of how the partial untwisting of the DNA double helix may induce the formation of local structures, such as cruciforms at inverted repeats or left-handed helicity for alternating purine-pyrimidine sections, that can be recognized by proteins.

The classic problem of predicting protein structure and function from sequence was discussed. Short of this goal, several approaches to predicting secondary structure from sequence were presented. R. Doolittle (University of California at San

*(continued on page 8)*

# Calendar of Genome Events

## 1989

### May

**4–5** GenBank advisors; Mountain View, CA

**18–20** European Molecular Biology Organization (EMBO) Workshop – Chromosome 21: Impact of the New Genome Technology in Human Genetics; Santa Margherita Ligure, Italy [*Nicoletta Sacchi, NCI, Frederick, MD (301) 698-5920*]

**24–26** X-Ray Microimaging for the Life Sciences; Lawrence Berkeley Laboratory, Berkeley, CA [*Shirley Ashley, (415) 486-6386, FTS 451-6386*]

### June

**8–9** Chromosome 16 Workshop; New Haven, CT [*Dr. Stephen Reeders, (203) 785-6737*]

**11–17** Tenth International Workshop on Human Gene Mapping (HGM 10); New Haven, CA [*Kristine Mooseker, (203) 786-5915*]

**19–20** National Institutes of Health (NIH) Program Advisory Committee on the Human Genome; Bethesda, MD

**22–23** National Institute of Child Health and Human Development (NICHD) Workshop on Chromosome 21; Bethesda, MD [*Evonne Williams, (301) 496-1383*]

**22–7/1** Human Genome Organization, International (HUGO); Moscow, U.S.S.R.

**27–30** Yeast Genetics and Molecular Biology (YGM) Meetings; Atlanta, GA [*Jean Francese, (301) 571-1825*]

**30–7/2** Genetics Society of America; Atlanta, GA [*Jean Francese, (301) 571-1825*]

### July

**6–7** First Canadian Workshop on BioInformatics; Ottawa, Ontario, Canada [*(613) 592-8160*]

**18** DOE Human Genome Steering Committee; Houston, TX

### August

**7–11** Gordon Research Conference on Molecular Genetics; Salve Regina College, Newport, RI [*A. M. Cruickshank, (401) 783-4011*]

**13–18** Macromolecules, Genes, and Computers: Chapter Two, International Symposium and Workshop; Waterville Valley, NH [*Temple Smith, (617) 732-3746*]

**24–26** Mouse Genome Workshop; Oxford, U.K. [*Mary Lyon, 44 (0235) 834393*]

### October

**2–4** Human Genome I: An International Conference on the Status and Future of Human Genome Research; San Diego, CA [*Scherago Assoc., Inc., (212) 730-1050*]

### November

**3–4** DOE Workshop for Contractors and Grantees in the DOE Human Genome Program; Santa Fe, NM

**5** DOE Human Genome Steering Committee; Santa Fe, NM

**12–15** American Society of Human Genetics (ASHG) Annual Meeting; Baltimore, MD [*Jean Francese, (301) 571-1825*]

### December

**4–5** NIH Program Advisory Committee on the Human Genome; Bethesda, MD

**Interface Workshop** *(from page 6)*

Diego) observed that approximately half of the protein sequences that are now being determined from nucleotide sequences are found to have significant similarities to other known proteins. A major issue concerned the extent to which exons correspond to functional domains of proteins.

In the past few years, many molecular biologists have come to regard computer databases and analysis programs as important components of their research; for some, as seen at this workshop, they are indispensable. Participants at this workshop were united in their belief in the importance of this field and in their appreciation for the meeting which provided communication and fostered collaborations in this highly interdisciplinary research.

The proceedings of the workshop will be published in *Computers and DNA*, edited by George I. Bell and published by Addison-Wesley (1-800-447-2226). ◇

*Submitted by Dr. George I. Bell*
*Los Alamos National Laboratory*

**Barnhart** *(from page 2)*

His career has centered on the genetic effects of radiation and chemical insults to cultured cells and DNA and to cellular processes that repair damaged DNA. Prior to joining DOE, he had been Visiting Associate Professor of Chemistry at the University of Missouri, Kansas City Campus; section head of the Genetic Toxicology and Microbiology Section at the Midwest Research Institute, Kansas City, Missouri; principal investigator and associate group leader of the Genetics Group and the program manager of the Mutagenesis Program of the Los Alamos National Laboratory.

Barnhart is a member of the American Society for Cell Biology, American Institute of Chemists, Radiation Research Society, and Sigma Xi (the Scientific Research Society). He is a past president and state counselor for the New Mexico Branch of the American Society of Microbiology and is currently president of the DOE/NRC Chapter of Sigma Xi. He received a B.A. in zoology/developmental biology from Indiana University and the Sc.D. in biochemistry/microbial genetics from Johns Hopkins University.

Barnhart may be contacted at DOE, Germantown, Maryland, at (301)353-5037, (FTS 233-5037). ◇

## Acronym Index

| | |
|---|---|
| **ANL** | Argonne National Laboratory, Argonne, IL |
| **DOE** | U.S. Department of Energy |
| **EMBL** | European Molecular Biology Laboratory, Heidelberg |
| **HERAC** | Health and Environmental Research Advisory Committee |
| **HGCTF** | Human Genome Computational Task Force |
| **HGSC** | Human Genome Steering Committee |
| **LANL** | Los Alamos National Laboratory, Los Alamos, NM |
| **LBL** | Lawrence Berkeley Laboratory, Berkeley, CA |
| **LLNL** | Lawrence Livermore National Laboratory, Livermore, CA |
| **NIH** | National Institutes of Health |
| **OHER** | DOE Office of Health and Environmental Research |
| **ORNL** | Oak Ridge National Laboratory, Oak Ridge, TN |

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