

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Frontiers of Science

Witness appearing before the
Senate Subcommittee on Labor-HHS-Education Appropriations

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Richard J. Turman, Deputy Assistant Secretary, Budget

Mr. Chairman and Members of the Committee:

I am pleased to present the Fiscal Year (FY) 2008 President's budget request for the National Human Genome Research Institute (NHGRI). The FY 2008 budget included \$484,436,000.

The theme of this hearing is "The Frontiers of Science." In leading the Human Genome Project, we at NHGRI have had the privilege of working at the frontiers for many years. And the projects I will describe today demonstrate how research at NHGRI is advancing ever more rapidly to catalyze a true revolution in medicine.

In February 2006, the Department of Health and Human Services announced the creation of two related groundbreaking initiatives in which NHGRI is playing a leading role. The Genetic Association Information Network (GAIN) and the Genes, Environment and Health Initiative (GEI) will accelerate research on the causes of common diseases such as asthma, schizophrenia, the common cancers, bipolar disease, diabetes, and Alzheimer's disease and help develop strategies for individualized prevention and treatment, thereby moving towards the possibility of personalized medicine.

GAIN is a public-private partnership among the NIH, the Foundation for the NIH, Pfizer, Affymetrix, Perlegen, the Broad Institute, and Abbott. GEI is a trans-NIH effort combining comprehensive genetic analysis and environmental technology development to understand the causes of common diseases. Both GEI and GAIN are powered by completion of the "HapMap," a detailed map of the 0.1 percent variation in the spelling of our DNA that is responsible for individual predispositions to health and disease. Beginning in FY2007, GAIN will produce data to narrow the hunt for genes involved in six common diseases and GEI will provide data for approximately another 15 disorders. Additionally, GEI will develop enhanced technologies and tools to measure environmental toxins, dietary intake and physical activity, and an individual's biological response to those influences.

ONGOING NHGRI INITIATIVES

Use of Comparative Genomics to Understand the Human Genome

NHGRI continues to support sequencing of the genomes of non-human species because of what they say about the human genome. The honey bee genome was published in the journal *Nature* in October. This bee's social behavior makes it an important model for understanding how genes regulate behavior, which may lead to important insights into depression, schizophrenia, or Alzheimer's disease. The genome of the sea urchin was sequenced and analyzed in November, revealing unexpected sophistication among its sensory and immune system genes.

Medical Sequencing

When it becomes affordable to sequence fully any individual's genome, the information obtained will allow estimates of future disease risk and improve the prevention, diagnosis, and treatment of disease. NHGRI is particularly interested in having a sequencing program that both drives technology and produces data useful to biomedical research. To this end, NHGRI has developed a medical sequencing program that utilizes DNA sequencing to: identify the genes responsible for dozens of relatively rare, single-gene diseases; sequence all of the genes on the X chromosome from affected individuals to identify the genes involved in X-linked diseases; and survey the range of variants in genes known to contribute to certain common diseases.

Sequencing technology advances, on the way to the \$1,000 genome

DNA sequencing enables a detailed ordering of the chemical building blocks, or bases, in a given stretch of DNA, and is a powerful engine for biomedical research. Though DNA sequencing costs have dropped by three orders of magnitude since the start of the Human Genome Project (HGP), sequencing an individual's complete genome for medical purposes is still prohibitively expensive. However, bold new advances in sequencing technology developed by NHGRI-funded researchers promise to reduce this cost greatly. NHGRI's ultimate vision is to cut the cost of whole-genome sequencing to \$1,000 or less. This could potentially enable sequencing of individual

genomes as part of routine medical care, providing health care professionals with a more accurate means to predict disease, personalize treatment, and preempt the occurrence of illness.

New findings in genetics of common disease

Technology development and new research approaches enabled by the HGP, the HapMap, and related NIH initiatives have led to important new understanding of the role of genetic factors in a number of common diseases. For instance, the Hap Map made possible research that recently identified two major genes that influence risk for developing adult macular degeneration, a leading cause of vision loss, with those at lowest risk having <1% chance of developing the disease, and those at highest risk a 50% chance (Klein et al., Science 2005; Yang et al., Science 2006). Other similarly derived recent discoveries include that variations in the genes *TCF7L2* (Helgasson et al., Nature Genetics 2007) and *SLC30A8* (Sladek et al. Nature 2007) elevate risk for developing type 2 diabetes, variations in the genes *IL23R* (Duerr et al., Science 2006) and *ATG16L1* (Hampe et al., Nature Genetics 2007) affect risk for Crohn's disease, a gene on chromosome 8 plays a role in prostate cancer, and the gene *SORL1* (Rogaeva et al., Nature Genetics 2007) plays a role in Alzheimer's disease. Each of these discoveries opens a new door toward prevention and treatment.

Knockout Mouse Project

The technology to "knockout" or inactivate genes in mouse embryonic stem cells has led to many insights into human biology and disease. However, gene knockout cells in mice have been made available to the research community for only about 10 percent of the estimated 20,000 mouse genes. Recognizing the wealth of information that mouse gene knockout cells provide, NHGRI coordinated an international meeting in 2003 to discuss the feasibility of a comprehensive project. These discussions have now resulted in a trans-NIH, coordinated, five-year cooperative research plan that will produce gene knockout cells in mice for every mouse gene and make these mice available as a community resource.

Chemical Genomics and the Molecular Libraries Roadmap Initiative

The NHGRI has taken a lead role in developing a trans-NIH chemical genomics. Part of the NIH Roadmap, this project offers public-sector researchers access to high throughput screening of libraries of small organic compounds that can be used as chemical probes to study the functions of genes, cells, and biological pathways. This powerful technology provides novel approaches to explore the functions of major cellular components in health and disease. In its first year, the ten centers in the Molecular Libraries Screening Centers Network entered screening data from 45 assays in the PubChem database at the National Library of Medicine. The team also published a new high-throughput screening approach that is speeding the production of data to be used to probe biological activities and identify leads for drug discovery.

NEW AND EXPANDED INITIATIVES

Population Genomics

To promote application of genomic knowledge to health, NHGRI recently established an Office of Population Genomics. The mission of the office is to stimulate multi-disciplinary epidemiology and genomics research and develop new resources for the study of common disease. It will take on challenges such as developing standards for genetic and phenotypic data and improved analytic strategies for relating them, stimulating novel research approaches, and supporting cross-disciplinary training to prepare researchers for new opportunities to improve health made possible through programs such as GEI and GAIN. This February, NHGRI's Advisory Council approved two new initiatives in this area. One funds development of a "basic tool set" for phenotypic and environmental exposure measurements in large-scale genomic research; the other supports existing biorepositories to conduct genome-scale studies with phenotype and environmental measures in electronic medical records. In the tradition of the HGP, the Office will promote widespread sharing of data, to stimulate the broadest possible application of knowledge and maximize public benefit.

The Cancer Genome Atlas (TCGA)

The Cancer Genome Atlas (TCGA) is a joint NCI-NHGRI effort to accelerate understanding of the molecular basis of cancer through application of genome analysis technologies. Technologies developed by the HGP and recent advances in cancer genetics have made it possible to envision mapping the changes in the human genome associated with all forms of cancer. TCGA began in 2006 with a three-year, \$100 million pilot project to determine the feasibility of a full-scale effort to explore the universe of genomic changes involved in all human cancers. Over the three years, NCI and NHGRI each plan to contribute a total of \$50 million. The first diseases being explored are glioblastoma multiforme, ovarian cancer, and squamous cell lung cancer. TCGA will provide (1) new insights into the biological basis of cancer; (2) new ways to predict which cancers will respond to which treatments; (3) new therapies to target cancer at its most vulnerable points; and, (4) new strategies to prevent cancer.

The Human Microbiome

There are more bacteria in the human gut than human cells in the entire human body. Furthermore, gut microbes have a profound effect on many human physiological processes, such as digestion and drug metabolism, and play a vital role in disease susceptibility and even obesity. The human microbiome project represents an exciting new research area for NHGRI, which, except for the bacterium *E. coli*, has focused its large-scale sequencing program on higher organisms rather than bacteria. Sequencing the genomes of 100 microorganisms that represent a significant, but unknown, fraction of all microbes in the human gut should provide a more complete picture of this aspect of human biology than has been available previously.

OTHER AREAS OF INTEREST

The U.S. Surgeon General's Family History Initiative

The family medical history is an effective and inexpensive means to determine more accurately an individual's risk for specific diseases; however, it is underutilized in health care. The U.S. Surgeon General's Family History Initiative was established to

focus attention on the importance of family history, and NHGRI has taken a lead role in this initiative. To further the effort in 2006, NHGRI selected the 12,000 employees at Brigham and Women's Hospital for a one-year demonstration project to educate and engage the health care community about the family history. To spread the importance of family history to the public, the software tool, "My Family Health Portrait," was enhanced for easier use, and resource materials were distributed to chronic disease and genetics experts in the state health departments of every U.S state and territory.

Genetic Discrimination

NHGRI remains concerned about the impact of potential genetic discrimination on research and clinical practice. A wealth of research has demonstrated that many Americans are concerned about the possible misuse of their genetic information by insurers or employers. The Genetic Information Nondiscrimination Act of 2007, S. 358, and its companion House bill, H.R. 493, are presently under consideration by the Congress. In 2005, the Administration supported S. 306, the Genetic Nondiscrimination Act of 2005. In January of this year, President Bush visited the NIH and reiterated the Administration's desire to see Congress pass a bill to protect Americans from genetic discrimination.

Thank you, Mr. Chairman. I hope I have offered you an informative view of the newest frontiers of science from the front lines of genomic science. I would be pleased to answer any questions that the Committee might have.

FRANCIS S. COLLINS, M.D., PH.D.

Director, National Human Genome Research Institute

Education:

University of Virginia, 1970 - B.S. (with Highest Honors);

Yale University, 1974 - Ph.D.;

University of North Carolina School of Medicine, 1977 - M.D. (with Honors)

Professional History:

1977-1981, Intern, Resident, Chief Resident in Medicine, North Carolina Memorial Hospital, Chapel Hill, North Carolina.

1981-1984, Fellow in Human Genetics and Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

1984-1993, Assistant, Associate and then Full Professor of Internal Medicine and Human Genetics, University of Michigan, Ann Arbor, Michigan.

1987-1993 Assistant, Associate and then Full Investigator, Howard Hughes Medical Institute.

1993 to present, Director, National Human Genome Research Institute, NIH, Bethesda, Maryland.

Biographical Information:

Dr. Collins is a physician-geneticist noted for his landmark discoveries of disease genes and his leadership of the Human Genome Project. With Dr. Collins at the helm, the Human Genome Project consistently met projected milestones ahead of schedule and under budget. This international project culminated in April 2003 with the completion of a finished sequence of the human genetic blueprint. From its outset in 1990, the public sequencing effort swiftly deposited all of its data into free, public databases for use by scientists around the world. Building on the foundation laid by the Human Genome Project, Dr. Collins is now leading the NHGRI effort to ensure that this new trove of sequence data is translated into powerful tools and thoughtful strategies to advance biological knowledge and improve human health.

Dr. Collins' own research initiatives have included the discovery of a number of important genes, including those responsible for cystic fibrosis, neurofibromatosis, Huntington's disease and most recently, the gene that causes Hutchinson-Gilford progeria syndrome, a dramatic form of premature aging. In addition to his scientific achievements, Dr. Collins is known for his continuing emphasis on the importance of ethical and legal issues in genetics. He has been a strong advocate for protecting the privacy of genetic information and has served as a national leader in efforts to prohibit gene-based insurance and employment discrimination.

Professional Organizations:

American Society of Human Genetics; American Society for Clinical Investigation; Association of American Physicians; Institute of Medicine; National Academy of Sciences; American Academy of Arts and Sciences.

Department of Health and Human Services
Office of Budget
Richard J. Turman

Mr. Turman is the Deputy Assistant Secretary for Budget, HHS. He joined federal service as a Presidential Management Intern in 1987 at the Office of Management and Budget, where he worked as a Budget Examiner and later as a Branch Chief. He has worked as a Legislative Assistant in the Senate, as the Director of Federal Relations for an association of research universities, and as the Associate Director for Budget of the National Institutes of Health. He received a Bachelor's Degree from the University of California, Santa Cruz, and a Masters in Public Policy from the University of California, Berkeley