National Human Genome Research Institute

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Fiscal Year 2011 Budget Request

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Mr. Chairman and Members of the Committee

I am pleased to present the Fiscal Year (FY) 2011 President's budget request for the National Human Genome Research Institute (NHGRI). The proposed FY 2011 budget is $533,959,000, an increase of $18,083,000 from the comparable FY 2010 enacted level of $515,876,000.

In the nearly ten years since the completion of the first draft sequence of the human genome, NHGRI has built on the foundation of the Human Genome Project and is now on track to create a future of genomic medicine. As we move beyond the first phase of the genomic revolution, we are approaching a time when doctors will select the best medicine for each patient based his/her own unique genome, when the genomic changes seen in a tumor will dictate the right course of cancer treatment, and when the genetic analysis of a sample in a doctor's office will quickly identify the bacteria relevant to a patient's disease. This isn't science fiction; this is the future that NHGRI is working to create.

Powerful New DNA Sequencing Technologies

The Human Genome Project succeeded because research-driven innovations led to dramatic developments of new technologies and massive reductions in the cost of sequencing DNA. Continued decreases in DNA sequencing costs are required to make genome sequencing part of routine clinical care. In order to focus attention on the challenges involved, NHGRI funds universities and companies to develop improved and more cost-effective DNA sequencing technologies through its $1,000 Genome program. NHGRI has further accelerated these efforts through funding provided by the American Recovery and Reinvestment Act of 2009. Multiple exciting new technologies are emerging and reaffirm the potential that-within a few short years-we will be able to routinely sequence a human genome for $1,000.

En route to applying genomics to medicine, there are continued efforts to fully understand the many mysteries about how the human genome actually works and how it encodes all the information involved in human biology. All of these programs extensively use these new DNA sequencing technologies. The ENCyclopedia of DNA Elements (ENCODE) project and comparative sequencing programs, among others, continue to extend our knowledge about the organization and function of the human genome. This type of basic research lays the foundation that is allowing us to learn how specific variants in our genomes can cause disease and, in turn, how best to design translational research programs.

Just as NHGRI-funded initiatives using these new DNA sequencing technologies lead to new breakthroughs, they are also revealing major challenges. Research groups that sequence genomes will soon be able to generate more data in a month than they previously did in a year. This dramatic acceleration in genome-sequencing projects is creating enormous datasets that strain even the most impressive information technology infrastructures. Meanwhile, the advances in DNA sequencing brought about by the $1,000 Genome program are greatly outpacing our abilities to analyze the generated data and to develop analytical strategies that will allow physicians to establish how to use genomic information to devise better treatment and prevention strategies. Addressing this data 'tsunami' is a high priority for genomics. NHGRI will continue to actively lead the scientific community in articulating the research and training needs and supporting the best opportunities to develop the computational infrastructure and tools necessary to assimilate, store, and analyze genomic data.

Linking Differences in Our Genomes to Disease

Over just the past few years, genetic studies have revealed hundreds of genomic variants that are associated with many common diseases, such as diabetes, heart disease, and cancer. These large-scale analyses point researchers to new locations within our genome harboring genes that are involved in disease pathology; understanding how these hundreds of genes work in healthy people and cause diseases when broken is now a high priority. Most genomic variants identified so far, however, only increase disease risk by a relatively small amount, indicating that there is still much to be discovered to fully understand the heritability of most common diseases. This knowledge will also be relevant for understanding population differences in disease prevalence across the globe, which is key for tackling many global health challenges. The NHGRI Center for Research on Genomics and Global Health is dedicated to studying the genetic contributions to common disease around the world and to extrapolating the knowledge gained for understanding health disparities.

In addition to these broad-based genomic studies seeking to implicate specific genetic factors with common diseases, a particularly unique NIH program- the Undiagnosed Disease Program (UDP) - is applying equally innovative strategies to study individuals whose rare disease has defied their doctors. UDP brings together physician-scientists across NIH to focus on one patient at a time. More than 240 patients have come to NIH hoping that this new integrated approach, which often includes detailed studies of the patient's genome, would produce a diagnosis and, perhaps, the delineation of a new disease. This program highlights the ability of NHGRI and NIH to interdigitate the clinic and the laboratory in a fashion that can lead to the discovery of new diseases.

Genomic Medicine

Congress established NHGRI to solve myriad technical challenges inherent to large-scale studies of the human genome. For this reason, the Institute has considered the development and dissemination of genomic technologies a core component of its research mission. In this spirit, the NIH Chemical Genomic Center (NCGC) and the recently launched Therapeutics for Rare and Neglected Diseases (TRND) initiatives are bringing high-throughput genomic strategies to bear on the drug development process. Both programs seek to transform existing paradigms in the early

stages of therapeutic development through innovative collaborations with public and private stakeholders. Broad sharing of the knowledge and data generated is a fundamental principle for TRND and NCGC as it maximizes the public benefit achievable through the NIH investment.

Increasingly, we are seeing opportunities where genomics research also can be translated in a fashion that will improve the practice of medicine in the clinic. By sequencing the entire genome of individual patients, researchers can pinpoint common and rare genetic variants that increase the risk of disease. Using the state-of-the-art NIH Clinical Center and the NIH Intramural Sequencing Center (NISC), the NHGRI ClinSeq project is investigating how best to integrate genome sequencing into the diagnosis and treatment of cardiovascular disease, the leading cause of death for both men and women in the United States. Meanwhile, the NHGRI Multiplex Initiative has been offering genetic susceptibility testing to a group of patients for several common health conditions to learn how people respond to genetic testing and the receipt of genetic information relevant to their health. The knowledge gained from research projects like ClinSeq and Multiplex will help establish how to generate and convey personal genomic information to individuals, initially in a clinical research setting and eventually as part of standard clinical care.

In the area of cancer research, The Cancer Genome Atlas (TCGA), a collaboration between NHGRI and the National Cancer Institute, is using the most advanced DNA sequencing technologies to decipher the diseased genomes found in cancer. By fully cataloging the genetic changes found in different cancer types, powerful new insights about how cancer develops will emerge and yield more robust abilities to classify tumor subtypes based on genomic information; such stratification can lead to more rational decisions about the best treatment for each tumor. For example, recent results from TCGA have led to a new ability to divide the most malignant form of brain cancer into four subtypes that each responds differently to therapy. TCGA's goal is to discover most, if not all, of the genetic alterations found in 50 of the most common forms of cancer; such knowledge offers the potential to revolutionize cancer diagnosis and treatment.

Another fascinating example of applying the latest genomic technologies to study human disease is the Human Microbiome Project (HMP). In contrast to studying the genetic glitches in human cells, HMP is developing a comprehensive inventory of the microbes (bacteria, fungi, and viruses) that live on and in the human body. These microorganisms outnumber our own cells 10 to 1, but the great majority of them cannot be isolated for study in the laboratory. As a result, relatively little is known about the types or proportions of microbes that inhabit different parts of the body and, importantly, how they interact with human cells to affect health. Early results demonstrate that body location (for example, the ear or elbow) has the greatest influence on microbial diversity; that is, the group of microbes living on the ear lobe of two different individuals will have more in common than the groups on one person's ear and that same person's elbow. This type of information, among other data that the HMP is generating, will help researchers dissect the complex genetic and microbial influences on a range of human diseases, from eczema to gastrointestinal disease. Through the HMP, we are already gaining a much more sophisticated view about the role that previously undetected microbes play in preventing and exacerbating human diseases.

Moving Forward

NHGRI continues to advance the promise of genomic medicine toward reality. Fundamental to this transition are the ongoing deliberations about the ethical questions raised by increasing genomic knowledge. NHGRI's diverse and robust portfolio of basic, translational, and ethics research in genomics continues to stretch the frontiers of discovery and medicine. To guide the genomics field in the coming years, NHGRI will complete a strategic planning process in 2010 that will provide a diverse and innovative research agenda for gaining an ever-growing understanding of the human genome; for continuing to advance human health in an ethical and equitable manner; and for moving us ever closer to a future of personalized genomic medicine that only a decade ago sounded like science fiction.

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Eric D. Green, M.D., Ph.D. is the Director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH) in Bethesda, Maryland, a position he had held since late 2009. Previously, he served as the NHGRI Scientific Director (2002-2009), Chief of the NHGRI Genome Technology Branch (1996-2009), and Director of the NIH Intramural Sequencing Center (1997-2009).

Born and raised in St. Louis, Missouri, Dr. Green received his B.S. degree in Bacteriology from the University of Wisconsin-Madison in 1981, and his M.D. and Ph.D. degrees from Washington University in 1987. During residency training in clinical pathology (laboratory medicine), he worked in the laboratory of Dr. Maynard Olson, where he launched his genomics research program. In 1992, he was appointed an assistant professor of pathology and genetics as well as a co-investigator in the Human Genome Center at Washington University. In 1994, he joined the newly established Intramural Program of the National Center for Human Genome Research at the NIH, later renamed the National Human Genome Research Institute.

Honors given to Dr. Green include a Helen Hay Whitney Postdoctoral Research Fellowship (1989-1990), a Lucille P. Markey Scholar Award in Biomedical Science (1990-1994), induction into the American Society for Clinical Investigation (2002), the Lillian M. Gilbreth Lectureship for Young Engineers at the National Academy of Engineering (2001), an Alumni Achievement Award from Washington University School of Medicine (2005), and induction into the Americal Association of Physicians (in 2007). He is a Founding Editor of the journal Genome Research (1995-present) and a Series Editor of *Genome Analysis: A Laboratory Manual* (1994-1998), both published by Cold Spring Harbor Laboratory Press. He is also Co-Editor of *Annual Review of Genomics and Human Genetics* (since 2005). Dr. Green has authored and co-authored over 250 scientific publications.

Since the early 1990s, Dr. Green's research program has been at the forefront of efforts to map, sequence, and understand eukaryotic genomes. His work included significant, start-to-finish involvement in the Human Genome Project. More recently, Dr. Green established a program in comparative genomics that involves the generation and comparative analyses of sequences from targeted genomic regions in multiple evolutionarily diverse species. The resulting data sets are providing new insights about vertebrate genome organization and evolution, and are revealing how conserved sequences can be used to identify functional genomic elements. His laboratory has utilized its own mapping and sequence data to identify and characterize several human disease genes, including those implicated in certain forms of hereditary deafness, vascular disease, and inherited peripheral neuropathy. Most recently, Dr. Green is leading a number of efforts that utilize contemporary strategies for large-scale DNA sequencing to study genomic variation among humans (in particular, that related to genetic disease) and to examine the microbial communities (i.e., the microbiomes) that exist in and on the human body.

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