

Department of Health and Human Services National Institutes of Health

Fiscal Year 2012 Budget Request

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Mr. Chairman and Members of the Committee

I am pleased to present the Fiscal Year (FY) 2012 President's budget request for the National Human Genome Research Institute (NHGRI). The proposed FY 2012 budget is \$524,807,000, an increase of \$13,749,000 from the comparable FY 2011 level of \$511,058,000.

This is an exciting time for biomedical research in general and for genomics research in particular. NHGRI investments in the development of genomic technologies and their application are generating innovative and powerful approaches to address a diverse array of biological and biomedical questions. In early 2011, after two-plus years of rigorous consultation and planning, NHGRI published a new strategic plan for the field of genomics in the premiere scientific journal *Nature*. This comprehensive strategic vision describes the next key steps in the herculean journey to decipher the secrets within our genetic code and to use those discoveries to empower health practitioners and patients in a fashion that leads to improved human health. The strategic plan also challenges the broader biomedical community to anticipate the scientific and non-scientific achievements that will be necessary to implement cost-effective and accessible genomics-based medical care (i.e., genomic medicine).

Enabling Research

Basic research lays the foundation for understanding the functional features within our genome and how disruptions in them can lead to disease. In fact, the knowledge gained from basic genomic investigations enables scientists and clinical investigators from other disciplines to pursue translational research programs to understand particular biological pathways or address disease-specific questions. The ENCyclopedia of DNA Elements (ENCODE) project and the related model organism ENCODE (modENCODE) project are moving forward effectively toward their goals of finding all the functional elements in the human genome, as well as in the genomes of organisms that serve as important models for human biology.

To stimulate and accelerate multi-disciplinary research, NHGRI has funded several Centers of Excellence in Genomic Science (CEGS). In addition to pursuing cutting-edge genomics research questions, these centers are associated with rigorous training programs that focus on groups under-represented in biomedical research. Such efforts aim to reinvigorate the biomedical research community by engaging diverse expertise and fostering the development of versatile young scientists.

The unprecedented decreases in the cost of DNA sequencing resulting from the NHGRI-stimulated technology development efforts are moving us steadily closer to the reality of using genome sequencing as a routine part of clinical care. However, even with the three-to-four orders-of-magnitude drop in DNA sequencing costs that has occurred, sequencing an entire human genome remains too expensive for the kind of human research studies needed to dissect the small genetic differences between individuals that contribute to increased risk for common diseases, such as cancer, heart disease, and asthma, because such work often requires the study of thousands or tens of thousands of individuals. To this end, NHGRI continues to push forward technology-development initiatives, such as the \$1,000 Genome program, to develop novel and even more cost-effective DNA sequencing methods. Concurrently, the NHGRI-funded large-scale sequencing centers continue to use innovative approaches for improving available DNA sequencing technologies. These efforts are projected to result in a substantial drop in the cost of generating a human genome sequence- to less than \$25,000 by the end of FY 2011 and less than or equal to \$15,000 by the end of FY 2012.

To develop an appropriately broad catalog of information about the variation within the genomes of different individuals across the world, NHGRI continues to contribute substantially to the international 1000 Genomes Project. In addition, on behalf of NIH, NHGRI led the effort to launch a research partnership with the Wellcome Trust, called the Human Heredity and Health in Africa (H3Africa) Initiative. This new effort seeks to stimulate research within African laboratories to enable leading-edge genomic studies to be conducted across the continent. The knowledge gained through a deeper understanding of genomic variation in African populations will not only lead to improved abilities to study genetic diseases in those populations, but will enhance our understanding of the complex interplay between environmental and genetic factors that influence disease susceptibility and drug responses in many diverse populations.

Building a Framework for Translation

Building on the tools and knowledge created by these and other basic research programs, the joint NHGRI-National Cancer Institute (NCI) project, The Cancer Genome Atlas (TCGA), is providing important new insights into some of the most vexing forms of malignancy, including brain cancer and, more recently, acute myeloid leukemia and ovarian cancer. Results from TCGA and associated cancer genomics studies by NHGRI-funded investigators point to new therapeutic targets and, as recently reported in the *Journal of the American Medical Association*, demonstrate the potential for more precise modes of cancer diagnosis and treatment. As a flagship program for NIH translational research activities, TCGA is expanding its efforts and will focus on an additional 20 major cancers over the next five years.

Beginning in FY 2012, NHGRI will expand its large-scale genome sequencing and analysis portfolio to include centers that target the study of rare, single-gene (Mendelian) disorders using cutting-edge genomic technologies. Rare disease research already is benefiting from the new genomic technologies. For example, the causative genes for a pair of developmental disorders were discovered recently: Miller syndrome, which affects the development of the face and limbs, and Kabuki syndrome, which affects facial and cognitive development. These two discoveries represent the 'tip of the iceberg' with respect to the identification of altered genes that result in rare diseases, as reports of such

discoveries are published in the scientific literature almost weekly. Another new NHGRI initiative in FY 2012 will pilot the use of genome sequencing in clinical care settings, an important step towards implementing genomic medicine.

Complementing the genome sequencing initiatives, the NIH Therapeutics for Rare and Neglected Diseases (TRND) program, which is currently administered by NHGRI, aims to innovate and accelerate the drug development pathway for rare and neglected diseases. As the TRND pilot projects move toward their initial milestones, the first full-scale project portfolio will be launched in collaboration with external and internal partners. Likewise, the NIH Chemical Genomics Center (NCGC) continues to serve as a national resource for the generation of novel chemical "leads" to spur inventive directions in candidate drug and biological assay identification. This statement is submitted with the recognition of the Department's notification to the Congress of an NIH reorganization that would establish a new National Center for Advancing Translational Sciences (NCATS).

Early Opportunities for Genomic Medicine

The clinical promise of genomics requires strong foundational knowledge about the structure and biology of genomes as well as the biology of disease. Increasingly, genomics will be used to advance medical science and to improve the practice of medicine.

Cancer genomics (as previously discussed) and pharmacogenomics (or genomically-guided medication prescription) are anticipated to be leading-edge examples of genomic medicine. Successes of the latter include the use of genomic information for making decisions about administering the antiretroviral drug abacavir, now the standard of care for HIV-infected patients. Other promising examples of pharmacogenomics involve the use of patient genomic information to target the application and dose of tamoxifen to treat breast cancer, clopidogrel to treat cardiovascular disease, and the blood-thinner warfarin. For cancer genomics, it is expected that genomic profiling of tumors will become increasingly routine for making decisions about treatment strategies.

Major advances in the study of common, genetically complex diseases also have been seen recently. Over the past five years, more than 4,000 validated associations have been made between a genomic region and a common disease (or another specific trait). Studies that identify and provide evidence to support the value-added connections between genetic factors and observed phenotype (physical traits, clinical symptoms, etc.) require substantial investments in time, funding, and resources, but are fundamental to translating genomics investments into clinical applications. One such initiative, the Electronic Medical Records and Genomics (eMERGE) Network, aims to advance the efficiency of this scientific approach. This program will enter its second phase in late FY 2011, during which it will not only link patients' DNA to their electronic medical record information, but also will explore the challenges of using the information to inform clinical care in a respectful, responsible manner.

The new NHGRI strategic plan identified several critical cross-cutting elements that are integral to navigating successfully the path to genomic medicine: bioinformatics and computational biology, education and training, and the continued study of the societal implications of genomics. The major bottleneck in genome science is no longer data generation; rather, it is the computational analysis of data. Beyond the research setting, the public, and especially healthcare providers, need to become much more conversant in genomics. To help address the needs of healthcare professionals, NHGRI has launched online tools to support genetic and genomic training in health professional education programs, including bilingual case studies.

Moving forward, translating basic genomic knowledge to improve human health will continue to rely on innovative technology development, large-scale collaborative and, increasingly, multi-disciplinary efforts, and robust attention to the societal implications of genomic advances. Demonstrating utility and feasibility will be critical for widespread adoption of genomic medicine; the thresholds for defining benefit and harm will vary across stakeholders and cultural perspectives. However, overcoming the challenges that accompany such a paradigm-changing venture is within reach.

The research and related programs that NHGRI will pursue over the next year will continue to lay the groundwork for an era where individualized genomic medicine will become a reality, and the original promise of the Human Genome Project will be fulfilled.

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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), a position he has held since late 2009. NHGRI is the largest organization in the world solely dedicated to genomics research. 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 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 Research Program of the National Center for Human Genome Research, 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), induction into the Association of American Physicians (in 2007), and a Distinguished Alumni Award from Washington University (2010). 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 280 scientific publications.

While directing an independent research program for almost two decades, Dr. Green was 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; these initial efforts later blossomed into a highly productive program in comparative genomics that provided important insights about genome structure, function, and evolution.

Now, as Director of NHGRI, Dr. Green is responsible for providing overall leadership of the Institute's research portfolio and other initiatives; this requires significant coordination with other NIH components and funding agencies. Most recently, Dr. Green led NHGRI to the completion of a strategic planning process that yielded a new vision for the future of genomics research, entitled *Charting a course for genomic medicine from base pairs to bedside*  (Nature, 470:204-213, 2011).

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