

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2009 Budget Request

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

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National Heart, Lung, and Blood Institute

Accompanied by:

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July 16, 2008

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The Fiscal Year (FY) 2009 budget of \$2,924,942,000 includes an increase of \$2,830,000 over the FY 2008 appropriated level of \$2,922,112,000. The NHLBI provides leadership for a visionary and highly productive research program in heart, lung, and blood diseases. In December 2007, the Institute announced a new strategic plan to guide its next decade of research, training, and education to reduce the burden of the diseases under its purview. This statement describes the main elements of the plan and then focuses specifically on the Institute's many efforts to forge a scientific basis for a more personalized approach to medicine in the future and to translate research into practice.

THE NHLBI STRATEGIC PLAN

Thanks to the dedicated involvement of the communities it serves, the NHLBI recently completed development of a scientific working plan to guide its activities and initiatives in the near future. The plan outlines goals that broadly reflect complementary and interactive avenues of scientific discovery—basic, clinical, and translational research. This crosscutting, versus disease-specific, approach highlights areas where the NHLBI is well positioned to make major contributions through investigator-initiated research and through programs that enable and supplement investigator-initiated activities. *Shaping the Future of Research: A Strategic Plan for the National Heart, Lung, and Blood Institute* is available on the NHLBI Web site at <http://apps.nhlbi.nih.gov/strategicplan/>, and printed copies have been distributed widely.

In the area of basic research, the plan focuses on delineating normal and pathological biological mechanisms and exploiting the emerging understanding of them to identify biomarkers of disease. Such biomarkers—broadly defined as measurable indicators of genotype, normal or pathological processes, or responses to therapeutic

intervention—will facilitate identification of disease subtypes and point the way toward new molecular targets for diagnosis, treatment, and prevention.

The plan's clinical and translational research goals emphasize transmission of knowledge between basic and clinical research so that findings in one arena rapidly inform and stimulate research in others. More precise methods of diagnosing disease and predicting susceptibility and prognosis are expected to arise from application of new approaches from basic science laboratories. A critical challenge will be to develop individualized preventive and therapeutic regimens based on genetic makeup in combination with developmental and environmental exposures. Insights are already emerging, but robust and efficient means of validating both patient-focused and population-based treatments will be needed to establish an evidence base to guide medical practice.

The plan acknowledges the need to enhance understanding of the processes involved in translating research into practice and to use that understanding to enable improvements in public health and stimulate further scientific discovery. It places particular emphasis on conducting research on primary prevention and identifying interventions that work in real-world health-care practice. As well, continued development and evaluation of new approaches to communicate research advances to the public is an important priority for ensuring full and informed participation of individuals in their health care.

SETTING THE STAGE FOR PERSONALIZED MEDICINE

Considerable progress has been made in reducing the burden of illness, particularly in the area of cardiovascular diseases, through development of therapeutic and preventive strategies that are broadly applicable to the general population at risk. Now we have advanced to a point where it may soon be possible to develop vastly more sophisticated approaches tailored to individuals. The dream is to be able to prevent disease entirely and, short of that, to be able to offer each patient a precisely targeted drug or other intervention, at a carefully titrated dose, for exactly the proper

duration, without risking dangerous or troublesome side effects. One path to realization of this dream lies in developing a more complete and detailed understanding of the genetic basis of individual health and disease.

Technological advances that make it possible to identify millions of DNA sequence variations rapidly and inexpensively, and to correlate them with individual characteristics and health indicators (phenotypes), have fueled an explosion of interest in this area. The NHLBI is investing substantial resources to move the science along, capitalizing on vast amounts of data gathered over many years from cohort studies such as the landmark Framingham Heart Study. In 2007, the Institute conducted genotyping using about 550,000 SNPs (single-nucleotide polymorphisms, which are tiny variations in the DNA code) in over 9,300 people from three generations of Framingham study participants. The genetic data are being linked to an array of phenotypic information, including major risk factors such as blood pressure, serum cholesterol, fasting glucose, and cigarette use; biomarkers such as fibrinogen and c-reactive protein; electrocardiography measures; imaging measures that reveal nascent pathology; and data on clinical cardiovascular disease outcomes. The resulting research resource, known as the Framingham SHARe (SNP Health Association Resource), is being developed and maintained by the NIH National Center for Biotechnology Information in its Database of Genotype and Phenotype (dbGaP). This rich source of data will be made available—with appropriate privacy safeguards—to qualified investigators at no cost.

The Framingham SHARe is only the first of many NHLBI efforts to enable what are known as genome-wide association studies (GWAS)—projects that involve scanning markers across complete sets of DNA from many individuals to find genetic variations associated with diseases or conditions of interest. The Institute is moving rapidly to increase the diversity of its genotype-phenotype data resources. Thus, we have created the MESA SHARe, based on cohorts from the Multi-Ethnic Study of Atherosclerosis, a long-running multicenter study that includes Americans of African, Chinese, Hispanic, and European ancestry. The SHARe-Asthma Resource project or

SHARP is conducting a genome-wide analysis in adults and children who have participated in NHLBI's clinical research networks on asthma. The Candidate-gene Association Resource or CARE project includes plans to genotype one million SNPs in African American men and women and link the results with phenotypic data obtained from eight major epidemiological studies, including the Cooperative Study of Sickle Cell Disease and the Sleep Heart Health Study. The NHLBI has also undertaken genotyping of African American women who participated in the Women's Health Initiative, a project of great interest to many NIH components and the communities they serve.

The GWAS approach offers a powerful and unprecedented avenue to unravel the contribution of complex traits to common diseases, and it is clear that the richness of the data generated from these studies is far greater than could be explored by a single investigator or group of investigators. To ensure that the greatest possible public benefit accrues from our investment in GWAS, under terms and conditions consistent with the informed consent provided by research participants, the NIH has established a GWAS data-sharing policy for NIH-supported investigators (<http://grants.nih.gov/grants/gwas/>). I was pleased to lead my NIH colleagues in this effort and, now, I am honored to serve as co-chair of the NIH Senior Oversight Committee for GWAS studies. I believe that robust NIH leadership in all aspects of GWAS will enable a superior yield from this exciting approach and bring us closer to realizing the dream of personalized medicine.

PHARMACOGENOMICS MOVES CLOSER TO THE BEDSIDE

The long-term vision of creating a broad selection of custom-made therapies for individualized treatment is tantalizing, but a great deal of work needs to be done before it can be achieved. Much closer to near-term application is the use of pharmacogenomics—an understanding of how genetics explains individual differences in response to drugs—to guide prescribing decisions for agents currently on the market. A case in point is the use of the anticoagulant warfarin, a tricky drug to prescribe because too little or too much can produce serious problems and the dose requirement

varies widely from one patient to another. Research has identified two specific genetic variations that appear to account for much of the inter-individual variation in sensitivity to warfarin, and we are now moving forward with a clinical trial to evaluate the clinical efficacy of a genotype-guided prescribing strategy for warfarin therapy and to determine whether the increment in efficacy and safety warrants the cost of genetic testing. We fully expect that genetic stratification of patients will become the norm for trials to evaluate new drugs, and that genetic information will prove invaluable for the design of novel alternatives to existing drugs that are likely to be ineffective or harmful in genetically susceptible individuals.

BRIDGING RESEARCH AND PRACTICE

In the upcoming years, these and other research efforts will yield an extraordinary amount of new information that will fundamentally transform medical practice and call for innovative approaches to translation and dissemination. We must be prepared to make the most of it. In line with its strategic plan, the NHLBI has developed a new knowledge network approach to bridge the gap between discovery and delivery, identify areas that should be addressed by future research, and develop more effective approaches for synthesizing and organizing scientific evidence and moving it into practice. The first network, addressing cardiovascular diseases, will be implemented globally and make innovative use of new media technologies.

The NHLBI has also begun a new effort to develop comprehensive, evidence-based, integrated guidelines to assist primary care physicians in helping adult patients reduce their risk of cardiovascular diseases. The integrated approach will focus on all cardiovascular risk factors to reflect the complicated clinical scenarios that patients and physicians typically face. Expert panels are being convened to review available scientific evidence and update existing guidelines for the prevention, detection, evaluation, and treatment of high cholesterol, hypertension, and overweight/obesity. An important goal of both the integrative guidelines and the updates is to improve implementation, especially among high-risk and minority communities. Ensuring that the public benefits from its investment in biomedical research is, and has always been, our highest priority.

Elizabeth G. Nabel, M.D.
Director
National Heart, Lung, and Blood Institute
National Institutes of Health

Elizabeth G. Nabel, M.D., a native of St. Paul, Minnesota, received her M.D. from Cornell University Medical College in 1981. She completed an internship and residency in internal medicine followed by a clinical and research fellowship in cardiovascular medicine at Brigham and Women's Hospital, Harvard University. In 1987, she joined the faculty at the University of Michigan as an Assistant Professor of Medicine and rose through the ranks, becoming Director of the Cardiovascular Research Center in 1992, Professor of Medicine and Physiology in 1994, and Chief of the Division of Cardiology in 1997. A cardiologist with extensive clinical experience, Dr. Nabel has had a distinguished career as a researcher. While at the University of Michigan, she became known for her research on the molecular genetics of cardiovascular diseases.

Dr. Nabel joined the National Heart, Lung, and Blood Institute (NHLBI) in 1999 as the Institute's Scientific Director of Clinical Research. In 2005, Dr. Nabel became Director of the NHLBI where she oversees an extensive national research portfolio of basic and clinical research to prevent, diagnose, and treat heart, lung, and blood diseases. The Institute also conducts educational activities for health professionals, patients, and the general public.

Dr. Nabel has made many contributions to basic and clinical research on the pathogenesis and treatment of cardiovascular diseases. She has devoted several decades to exploring genes that contribute to vascular disease and strategies for gene transfer to benefit patients with those diseases. She has delineated the mechanisms that regulate the vascular proliferation and remodeling which lead to blood vessel blockages. Her research now focuses on the role of genetic factors in blood vessel

diseases, including atherosclerosis and Hutchinson Gilford Progeria Syndrome, a rare, premature aging syndrome.

Dr. Nabel has served as a Visiting Professor at major medical centers throughout the country and delivered major lectureships in Europe and Australia. She has received numerous awards for her scientific accomplishments, including the Willem Einthoven Award from Leiden University in the Netherlands, the Amgen-Scientific Achievement Award from the American Society for Biochemistry and Molecular Biology, and Distinguished Achievement Awards from the Basic Cardiovascular Sciences Council and the Atherosclerosis, Thrombosis, and Vascular Biology Council of the American Heart Association. In 2001, she received an honorary doctorate from the University of Leuven, Belgium and in 2006 from Mt. Sinai School of Medicine, New York.

Dr. Nabel is an elected member of the Institute of Medicine of the National Academy of Sciences, the American Society of Clinical Investigation, and the Association of American Physicians, as well as a Fellow of the American Heart Association and the American College of Cardiology. She serves on the editorial board of many scientific journals, including being an editorial board member of the *New England Journal of Medicine*, past Board of Reviewing Editors for *Science*, and associate editor for the *Journal of Clinical Investigation*.

A partner on 13 patents, Dr. Nabel is the author of more than 200 scientific publications, Elizabeth G. Nabel, M.D., a native of St. Paul, Minnesota, received her M.D. from Cornell University Medical College in 1981. She completed an internship and residency in internal medicine followed by a clinical and research fellowship in cardiovascular medicine at Brigham and Women's Hospital, Harvard University. In 1987, she joined the faculty at the University of Michigan as an Assistant Professor of Medicine and rose through the ranks, becoming Director of the Cardiovascular Research Center in 1992, Professor of Medicine and Physiology in 1994, and Chief of the Division of Cardiology in 1997. A cardiologist with extensive clinical experience, Dr. Nabel has had a distinguished career as a researcher. While at the University of

Michigan, she became known for her research on the molecular genetics of cardiovascular diseases.

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