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Two NIH Initiatives Launch Intensive Efforts to Determine Genetic and Environmental Roots of Common Diseases

*President's FY07 Budget Calls for \$40 Million a Year Boost for Multi-Year Effort;
Companies to Commit More Than \$25 Million to Launch Genetics Project This Summer*

WASHINGTON – Wed. Feb. 8, 2006 – The Department of Health and Human Services (HHS) today announced the creation of two new, closely related initiatives to speed up research on the causes of common diseases such as asthma, arthritis and Alzheimer's disease.

One initiative boosts funding at the National Institutes of Health (NIH) for a multi-institute effort to identify the genetic and environmental underpinnings of common illnesses. The other initiative launches a public-private partnership between NIH, the Foundation for the National Institutes of Health (FNIH) and major pharmaceutical and biotechnology companies, especially Pfizer Global Research & Development of New London, Conn.; and Affymetrix Inc. of Santa Clara, Calif., to accelerate genome association studies to find the genetic roots of widespread sicknesses. The genetic analysis component of the two initiatives is highly complementary.

Genes and Environment Initiative

HHS Secretary Mike Leavitt announced on Monday that the President's budget proposal for fiscal year (FY) 2007 includes \$68 million for the Genes and Environment Initiative (GEI), a research effort at NIH to combine a type of genetic analysis and environmental technology development to understand the causes of common diseases. The FY 2007 budget represents a \$40 million increase above the \$28 million already planned for these efforts in the NIH budget.

If approved by Congress, this additional federal funding will begin in FY 2007 and continue for multiple years. Of the first year's funding, \$26 million will go to genetic analysis and \$14 million for the development of new tools to measure environmental exposures that affect health.

“The discoveries made through these efforts will ultimately lead to profound advances in disease prevention and treatment,” Secretary Leavitt said. “These are the kinds of innovative efforts that we should support. We must seize the historic opportunity provided by the Human Genome Project and the International HapMap Project, to speed up the discovery of the genetic causes of common diseases like diabetes and hypertension. At the same time, it's critical that we also understand the environmental contributors to sickness, and the interplay among genes and environment. There is not a moment to be lost.”

GEI will have two main components: a laboratory procedure for efficiently analyzing genetic variation in groups of patients with specific illnesses and a technology development program to devise new ways of monitoring personal environmental exposures that interact with genetic variations and result in human diseases.

The proposed federal funding level will enable GEI to perform genetic analysis – or genotyping - studies for several dozen common diseases. The exact diseases to be studied will be determined by peer review. An initial survey of existing NIH-supported clinical studies identified more than 100 with sufficient numbers of already characterized patients to get this effort started. In addition, NIH expects to develop four new environmental monitoring devices a year.

“This initiative would not have been possible a year or two ago,” said Elias A. Zerhouni, M.D., Director of the National Institutes of Health, an agency within the Department of Health and Human Services. “This is a tangible result of the nation's increased investment in medical research over the past 10 years. We are now poised to combine what we have learned from years of population studies, with newly available technologies, developed with NIH support. These technologies reduced the cost of genotyping by more than 100-fold, making such a comprehensive effort affordable. Equally important, this effort will dramatically increase our understanding of the environmental factors of health and disease, and help us develop novel measures of gene-environment interactions. We stand on the threshold of creating a future that will revolutionize the practice of medicine by allowing us to predict disease, develop more precise therapies and, ultimately, pre-empt the development of disease in the first place.”

Public-Private Partnership

At the same time, a public-private partnership between NIH, FNIH, which is a non-profit foundation established by Congress to support the mission of the NIH; Pfizer and Affymetrix is being created to further accelerate this important research on the genetic association studies.

The new partnership, called the Genetic Association Information Network (GAIN), is being launched with a \$5 million donation from Pfizer to set up the management structure and \$15 million worth of laboratory studies to determine the genetic contributions to five common diseases. Affymetrix, a biotech company that develops the types of tools used in these kinds of genetic studies, will contribute enough laboratory resources to study two additional common diseases. On average, it costs about \$3 million to carry out one study.

“We’ve translated early information from genetic research into valuable medicines for HIV/AIDS, heart disease and the prevention of organ rejection,” said Martin Mackay, Ph.D., Senior Vice President Worldwide Research & Technology, Pfizer Research & Development. “But these advances have only scratched the surface of possible revolutionary approaches to treat and cure diseases. Pfizer, the NIH and other public/private biomedical research interests have complementary missions greater than the sum of their parts. Our hope is that this public/private initiative will encourage a deeper collective understanding of the genetic factors of disease for major new therapeutic advances.”

GAIN will be an FNIH-managed partnership that includes NIH, industry, foundations, individuals and advocacy groups. Governance will include an executive committee, a steering committee, as well as peer review and data access committees.

“Our partnership with pharmaceutical and biotech companies to speed up this research exemplifies the aim Congress had in mind when it established the Foundation for the National Institutes of Health to support the mission of NIH,” said John E. Porter, Vice Chairman of the foundation’s Board of Directors. “Through the financial support of the private sector, NIH will now be able to launch into this exciting initiative immediately. Moreover, the interaction of scientists from the public and the private sector dramatically increase the likelihood that this initiative will get off to a quick and efficient start that will genuinely produce important advances for all patients.”

Genetic Factors

The genetic analysis of both GAIN and GEI will focus on the alternative spellings – called single nucleotide polymorphisms or SNPs – that normally occur in the order of the 3 billion DNA base pairs or letters that make up a person’s genome. SNPs are like single-letter misspellings of a word. Most of these genetic variations are biologically meaningless. But a small fraction of these SNPs alter the function of a gene – often only slightly. The combination of many slightly altered genes may significantly increase the risk of a specific disease, but identifying such a complex set of genetics changes is challenging. Finding these disease-causing variants is one of the highest priorities of current biomedical research.

“Virtually all diseases have a hereditary component, transmitted from parent to child through the three billion DNA letters that make up the human genome,” said Francis S. Collins, M.D., Ph.D., Director of the National Human Genome Research Institute at NIH and chairman of the GAIN Steering Committee and co-chairman of the NIH Coordinating

Committee for GEI. “But progress in identifying the genetic factors that influence health or disease, or even the response to treatment, is difficult. Both initiatives promise to rapidly identify the myriad genes in an individual that, taken together, contribute to an increased risk of illness – or that increase the chances of a healthy life. As the genetic underpinnings of health and common diseases become clearer, researchers will be empowered to develop targeted treatments that either prevent illness from occurring or treat it effectively once it does.”

There are about 10 million common SNPs in the human population. Scanning the genomes of large numbers of patients for such a large number of variants would be prohibitively expensive. Fortunately, a major shortcut has been discovered that reduces the workload about 30-fold. The International HapMap Project, led by the NIH and completed in October 2005, demonstrated that the 10 million variants cluster into local neighborhoods, called haplotypes, and that they can be accurately sampled by as few as 300,000 carefully chosen SNPs. New technological systems allow these SNPs to be systematically studied in high-throughput facilities that dramatically lower the cost.

For each study of 1,000 to 2,000 patients with a specific disease and a similar number of people who do not have the illnesses (controls), an investment of \$3 million to \$6 million (depending on the number of patients and controls) is needed for the first stage of genotyping. Follow-up studies to validate the results with additional patients and controls, data analysis, and patient management expenses will add to these basic costs. It is important to note, however, that these costs are a small fraction of what has already been invested in enrolling these study subjects, examining them, carrying out extensive laboratory investigations, and collecting their DNA.

The genotyping work itself will be performed by either commercial or government laboratories. The initial GAIN genotyping supported by Pfizer will be carried out by Perlegen Sciences, Inc., of Mountain View, Calif., and will start in late summer 2006; Pfizer is contributing these Perlegen-produced genotypes as an “in kind” donation to the project. A similar arrangement will be worked out with Affymetrix. Federally funded genotyping for GEI will be managed by an NIH coordinating committee under the usual government rules, subject to competition between research facilities, and begin in FY 2007.

The research will lead directly to the identification of major genetic susceptibility factors for common diseases of substantial public health impact – disorders such as heart disease, diabetes, cancer, stroke, Alzheimer’s disease, schizophrenia, osteoporosis, asthma, cataracts, hypertension, Parkinson’s disease, autism and obesity. The target diseases and the populations studied have yet to be selected and will be subject to a peer-review process.

Environmental Factors

Genes alone do not tell the whole story. Recent increases in chronic diseases like diabetes, childhood asthma, obesity or autism cannot be due to major shifts in the human gene pool. They must be due to changes in the environment, including diet and physical activity, which may produce disease in genetically predisposed persons. Therefore, GEI will also invest in innovative new technologies to measure environmental toxins, dietary

intake and physical activity, and to determine an individual's biological response to those influences, using new tools of genomics, proteomics and metabolomics.

“Differences in our genetic makeup certainly influence our risks of developing various illnesses,” said David A. Schwartz, M.D., Director of the National Institute of Environmental Health Sciences, also part of NIH, and co-chairman of the NIH Coordinating Committee for GEI. We only have to look at family medical histories to know that is true. But whether a genetic predisposition actually makes a person sick depends on the interaction between genes and the environment. We need better tools to evaluate environmental exposures, dietary intake and activity levels, and then to determine how those risk factors interact with specific genotypes to either maintain health or lead to disease. Without these more precise measures of exposure, it will be very difficult to figure out why certain people develop disease and others do not. We also need to find out why a disease has such a different prognosis from one person to the next. Given the recent advances in biomedical research, this is the right time to take on this challenge.”

To determine how the environment, diet and physical activity contribute to illness, investments will be made in emerging technologies, such as small, wearable sensors that can measure environmental agents that have contact with the body and individual measures of activity. Devices also will be developed that measure changes in human biology, which can be observed in samples of blood or urine. In aggregate, these new tests will provide the precision needed to help determine how these factors influence the genetic risk of developing disease. The goal is to produce devices for application to eventual population studies, to speed up data processing, to enhance accuracy and to reduce cost.

With the \$14 million annual investment in the environmental component of this initiative, NIH will develop technologically advanced measures of dietary intake, precise personalized measures of physical activity, and biological measures that identify prior exposures to potential toxins such as metals and solvents. NIH also will assess disease indicators like inflammation and oxidative stress that are known to be influenced by environmental toxins.

The National Center for Biotechnology Information, a part of the National Library of Medicine at NIH, will develop databases to manage the vast amount of genetic, medical and environmental information that will emerge from these initiatives. To encourage rapid research advances, and in keeping with the principles pioneered by the Human Genome Project and increasingly common in such pre-competitive public/private partnerships, all data generated through these initiatives will be placed in the public domain.

Background information on whole genome association studies can be found at www.genome.gov/17516714. Background information on environmental impacts on health can be found at www.genome.gov/17516715.

The National Institutes of Health (NIH), the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U. S. Department of Health and Human Services. Several institutes that study specific diseases will participate

in the initiative. It is the primary Federal agency for conducting and supporting basic, clinical, and translational medical research, and it investigates the causes, treatments and cures for both common and rare diseases. For more information about NIH and its programs, visit <http://www.nih.gov>.

The Foundation for the National Institutes of Health is a nonprofit organization authorized by Congress to raise private funds and establish public-private partnerships to support the NIH mission. More information about FNIH can be found at <http://www.fnih.org/>.

Pfizer Global Research & Development is the world's largest privately owned biomedical research organization. Pfizer Inc discovers, develops, manufactures and markets leading prescription medicines, for humans and animals, and many of the world's best-known consumer brands. More information about Pfizer can be found at <http://www.pfizer.com>

NOTE: The initiatives will be announced at a press conference at 9 a.m. Wednesday, Feb. 8, 2006, in the Murrow Room of the National Press Club, 529 14th Street NW, Washington, D.C. A webcast of the press conference will be available two to three hours after its conclusion at <http://videocast.nih.gov/ram/nhgri020806.ram>.

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