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I. Introduction

Good Morning Chairman Pitts and Members of the Subcommittee. I am Francis S. Collins, Director of the National Institutes of Health (NIH), an agency of the U.S. Department of Health and Human Services (HHS).

Due to the steadfast support of this Administration, the Subcommittee, Congress, and the American people, NIH continues to be the most prestigious biomedical research agency in the world. I thank each of you for your continued support of NIH's mission to seek fundamental knowledge about the nature of living systems and to apply it in ways that enhance human health, lengthen life, and reduce suffering from illness and disability.

I have been asked to update you on the implementation of the NIH Reform Act of 2006 (Public Law 109-482), review how NIH sets scientific priorities at a time of unprecedented scientific opportunity, and report on the new National Center for Advancing Translational Sciences (NCATS). I welcome this opportunity to appear before you and brief you on some of what NIH has accomplished and what we hope to achieve to address the devastating burdens of disease and disability.

NIH Facts and Figures:

NIH is the largest funder of biomedical research in the world and our FY 2012 budget is $30.86 billion. NIH's extramural research program represents 83 percent of our budget and supports about 50,000 research projects and research training awards and more than 300,000 scientists and research personnel at more than 2,600 universities, medical schools, and other research institutions in the United States. Every

state, along with nearly every Congressional district, receives NIH research funding. Approximately 11 percent of our budget funds nearly 7,000 intramural scientists working at the NIH campus in Bethesda, in laboratories in Baltimore, Rockville and Frederick, Maryland; at Research Triangle Park near Raleigh, North Carolina; at the Phoenix Epidemiology and Clinical Research Branch in Phoenix, Arizona; and at the Rocky Mountain Laboratories in Hamilton, Montana.

Public Health Benefits:

NIH basic research and translational and clinical advances have sparked a revolution in the diagnosis, treatment, and prevention of disease. Biomedical research funded by NIH has prevented immeasurable human suffering and yielded economic benefits as well as helping tens of thousands of U.S. citizens live longer, healthier, and more productive lives. These benefits include:

- a nearly 70 percent reduction in the death rate for coronary disease and stroke in the last half century;
- a nearly 30 percent decline over the last three decades in the age-standardized prevalence of chronic disability among American seniors;
- a 40 percent decline in infant mortality over 20 years; and
- more than 150 FDA-approved drugs and vaccines, or new uses of existing drugs.[1]

Just a month ago, the Centers for Disease Control and Prevention (CDC) reported that among U.S. adults who suffer from diabetes, cardiovascular disease-related death declined by 40 percent and mortality from all causes declined by 23 percent between 1997 and 2006.[2] This drop in deaths due to diabetes is encouraging and is in large

[1] Stevens, A.J., *et al.,* "The Role of Public-Sector Research in the Discovery of Drugs and Vaccines." *N. Engl. J. Med*., 364: 535-41, 2011.

[2] Gregg EW, Garfield S, Cheng YJ, Geiss L, Saydah S, Barker, L, Cowie C. Trends in Death Rates Among U.S. Adults With and Without Diabetes Between 1997-2006. Diabetes Care 2012; 35: 1252-1257.

measure due to NIH-funded research that has enabled us to better understand and manage this disease.[3] But it also underscores the urgency of NIH's research mission: we must fight the obesity epidemic in our population and prevent type 2 diabetes in the first place. We will not prevail against these twinned epidemics of obesity and diabetes without research supported and performed by NIH.

II. Implementation of NIH Reform Act of 2006

About six years ago, this Committee began work on an ambitious reauthorization of the NIH. The Committee's goals were clear: give NIH's scientific leadership greater flexibility to pursue emerging research opportunities, create new mechanisms and structures to enable swift and frictionless collaboration among NIH's 27 institutes and centers, and increase the transparency in NIH's portfolio and the accountability of its scientific management.

Today I can report that we are using new structures and mechanisms to enable and expedite trans-NIH research managed by the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) and funded by the Common Fund. We have increased transparency with online research inventories and portfolio databases. And we have worked closely with the Scientific Management Review Board (SMRB), instituted by the Reform Act, which has proven an effective advisor for providing expert advice about NIH's organization, management, and performance.

[3] UnitedHealth Center for Health Reform & Modernization (2010). The United States of Diabetes: Challenges and opportunities in the decade ahead. Working Paper 5, November 2010. (http://www.unitedhealthgroup.com/hrm/unh_workingpaper5.pdf)

DPCPSI and the Common Fund:

The NIH Reform Act established DPCPSI to identify research that addresses important areas of emerging scientific opportunity, emerging public health challenges, and knowledge gaps. Research addressed by DPCPSI must merit special emphasis, benefit from additional research involving collaboration between two or more institutes or centers, or otherwise benefit from strategic coordination and planning. The Act also authorized the Common Fund, which includes programs from the former NIH Roadmap for Medical Research, to support this innovative research. The Common Fund was developed to change the way research is conducted – the way investigators approach their work, the tools they use, and the data and resources that are available to them. As the first Roadmap programs are reaching their tenth and final year, payoffs are beginning to be realized and the academic research culture has changed as investigators now routinely embrace interdisciplinary, multi-investigator-led projects. The Common Fund programs are transformative, synergistic, catalytic, crosscutting and unique.

Each year, NIH initiates a strategic planning process to identify the most pressing research needs and the most compelling scientific opportunities to support via the Common Fund. Gathering input from NIH stakeholders is a critical part of this process, as is an assessment of the current research portfolio. Through the Common Fund, NIH has funded the development of tools, technologies, data sets, and fundamental science that are relevant to health research broadly. The Common Fund now supports over 20 programs. Most of these programs consist of a series of integrated initiatives that collectively address a set of goals that aim to transform the way research is conducted,

the way that health and disease are understood, and the way that diseases are diagnosed or treated. Some examples include:

- The Human Microbiome Project (HMP) is systematically exploring the complex array of microorganisms that live on and in the human body, and play a critical role in health and disease. The HMP has developed a reference collection of 178 microbial genomes, including 30,000 newly discovered proteins as a resource for the scientific community. Demonstration projects have identified correlations between disturbances in the microbiome and diverse illnesses such as neonatal intestinal disease, cystic fibrosis, obstructive lung disease, and chronic sinusitis.

- The Patient-Reported Outcomes Measurement Information System (PROMIS) program has developed tools for the quantitative measurement of patient-reported outcomes for an array of diseases and conditions, including pain, depression, and fatigue. The PROMIS tool quickly is becoming the standard for measuring patient-reported outcomes during clinical studies.

- The Structural Biology program is pioneering new technologies to enable structural determination of proteins embedded in cell surfaces. These proteins represent the vast majority of targets for drugs but have been difficult to analyze. This Common Fund program is developing methods for the purification and analysis of these proteins which are helping in the design of new drugs. For example, a collaboration between researchers from the Structural Biology program and the Molecular Libraries program led to the discovery of a new drug that has completed phase 1 safety trials and is now in phase 2 trials for multiple sclerosis and inflammatory bowel disease.

- The Interdisciplinary Research program tested new mechanisms of fostering novel approaches to complex problems through interdisciplinary science. For example, the NeuroTherapeutics Research Institute involved scientists from disciplines such as neurology, neurophysiology, developmental pediatrics, psychiatry, chemistry, and mouse behavior to investigate the neurodegenerative disease Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), which causes tremors, imbalance, and dementia. These researchers discovered that in a mouse model of FXTAS, damage to neurons is evident early in life, highlighting the need to develop early biological, chemical, and behavioral interventions despite the appearance of symptoms later in life.

The Common Fund's High Risk/High Reward (HRHR) Program is another exciting initiative, which dedicates funding to foster innovation and creativity. HRHR enables the Common Fund to function like a "venture capital space" and support research that may

be considered unconventional and high-risk, but if successful, might transform our understanding of a wide range of biomedical problems, develop transformative tools and methods, or establish new clinical paradigms. The HRHR program emphasizes early stage investigators, who often have the most innovative ideas, but don't have the research "track record" to qualify for funding from more traditional grant mechanisms.

The Pioneer Award is designed to support a small number of investigators of exceptional creativity who propose bold and highly innovative new research approaches that have the potential to produce a major impact on broad, important problems in biomedical and behavioral research. The New Innovator Award program supports extraordinarily creative investigators within ten years of their M.D. or Ph.D. degree who have high impact research ideas but lack the preliminary data required for a traditional research project grant. The Early Independence Award allows exceptional scientists to "skip the post-doc" and move into independent research positions immediately after the completion of their graduate degrees. Outstanding scientists supported by these programs who have made notable contributions to research in a variety of scientific fields include:

- Karl Deisseroth, Pioneer Awardee: developed a set of tools to control subpopulations of neurons in the brain using light, in order to elucidate the precise brain circuitry that is affected in brain injury, Parkinson's disease, and many psychiatric diseases.
- Nathan Wolfe, Pioneer Awardee: established a surveillance system to monitor the entry of novel viruses into the human species, which may pose a significant threat to global public health.
- Adah Almutairi, New Innovator Awardee: developed a new "smart" polymeric material that could have widespread applications in drug delivery, surgical procedures, and medical implants.
- Aydogan Ozcan, New Innovator Awardee: created a portable, inexpensive, lensless microscope that can fit on mobile cell phones and be used to test for

pathogens in blood and water samples in remote regions where medical facilities are scarce.

Fostering innovation is a theme throughout the Common Fund. While this is an explicit goal of the High Risk/High Reward set of initiatives, it is an overarching goal of all of the programs. This investment in innovation is paying off economically, as well as scientifically, with patent applications, commercialization of technologies, and growth of new sectors in biomedical research. An Outcome Evaluation of the Pioneer Award Program revealed that three of the 22 awardees from the first two years of the initiative have applied for patents arising from their Pioneer research, and a fourth has licensed his technology for commercialization. Another Common Fund program, the Bridging Interventional Development Gaps program (formerly the Rapid Access to Interventional Development program) has led to 11 Investigational New Drugs, five of which have been licensed to companies for further development. The Molecular Libraries program has also led to many patent applications, and one molecule discovered through this program is now being tested in a clinical trial. This program has also contributed to a culture change in academic research by enabling all investigators to have access to chemical screening facilities equivalent to those of the pharmaceutical industry. Molecular screening centers have proliferated beyond the Common Fund set of centers, such that a 2010 evaluation indicated that 48 centers exist outside the Common Fund programs. This exemplifies how Common Fund programs can have significant impact beyond the immediate boundaries of their awards.

Transparency:

As directed by the Reform Act, NIH successfully implemented electronic systems to code uniformly the research grants and activities of all NIH institutes and centers. The Research, Condition, and Disease Categorization (RCDC) system provides consistent and readily-accessible information to the public about NIH-funded research, providing a complete list of all NIH-funded projects, beginning with fiscal year 2008, in each of 233 reported categories of disease, condition, or research area. We also created the Research Portfolio Online Reporting Tool (RePORT) which provides public access to reports, data, and analyses of NIH research activities, including information on NIH expenditures and the results of NIH supported research. By developing these tools, we provide better, more consistent and more accessible information about our research.

Management Review:

Finally, the SMRB established by the Reform Act issues reports detailing recommendations to the appropriate agency officials, both at NIH and HHS, on whether and to what extent their organizational authorities should be used. The reports are then submitted to the Congress by the NIH Director. Since its first meeting in April of 2009, the Board has held 11 meetings and produced four reports; one of which made recommendations about how the NIH can best contribute to advancing the translational sciences. Most recently, the Board agreed to undertake an analysis of the NIH Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs—namely, to recommend strategies for how NIH can optimize its use of these funding mechanisms. Deliberations on this topic are just underway and will continue throughout next year.

III. Priority Setting:

With the responsibility to set scientific priorities comes an obligation to explain how we do this and demonstrate that we are being good stewards of taxpayer dollars. Let me discuss the four principles that govern how we set our research priorities.

First and foremost, NIH responds to public health needs. These needs, whether an emerging infectious disease or the growing burden of chronic disease management on patients, our health care system and our economy, are addressed through a complex balance among basic, translational, and clinical sciences. The incidence, severity, cost, and sheer human suffering associated with specific conditions are also factors in how we set research priorities.

Secondly, NIH applies stringent critical peer review, provided by outside scientists who are experts in a given field, to rank the scientific opportunity and quality represented by the research proposals submitted. This intense competition has always assured that NIH research is of the highest scientific quality.

Thirdly, scientific history has repeatedly demonstrated that significant research advances occur when new findings, often completely unexpected, open up new experimental possibilities and pathways. We constantly are assessing our research portfolio in light of what the latest science suggests. Frustratingly, not all disease or scientific problems are equally ripe for new advances, nor do such advances come at the same rate across the portfolio, no matter how pressing they might be for the public's health.

Finally, we strive to ensure the diversity of NIH's research portfolio. We simply cannot predict the next scientific revelation or anticipate the next opportunity. If you think of scientific priority-setting as a series of thousands of doors that we might open—when we cannot know what is behind any one door—you can appreciate the challenge of setting priorities and the need for a broad research portfolio.

IV. Technology is Driving Science: NCATS as NIH Response

The new structures, mechanisms, and flexibility given to NIH by the Reform Act came at an especially opportune moment in scientific history. The technological revolution that we are seeing in biomedical research and the flexibilities have enabled us to respond more nimbly to what I consider the major challenge in getting therapies to patients. Let me talk about technology first.

In his biography, Apple founder Steve Jobs is quoted as saying that a "silver lining" in his battle with pancreatic cancer was that his son Reed had been able to "spend a lot of time studying with some very good doctors." Jobs goes on to say that his son's enthusiasm for biomedical research:

> *. . . is exactly how I felt about computers when I was his age. I think the biggest innovations of the twenty-first century will be the intersection of biology and technology. A new era is beginning, just like the digital one was when I was his age.*[4]

Jobs was correct: today technological advances are driving science. We need look no further than the cost of DNA sequencing to see this dynamic at work. The cost

[4] Isaakson, Walter, Steve Jobs (New York: Simon & Schuster, 2011) 539.

curve for sequencing is dropping at a breathtaking rate; sequencing speed has increased even faster than computer processing speed. What's more, the average cost of sequencing an entire genome has fallen from about $3 billion 12 years ago, to $10 million five years ago, to about $7,700 today. Two U.S. companies recently announced that they are manufacturing machines that will sequence an individual's genome for approximately $1,000, and that the first such instruments will go on sale before year's end. Lower sequencing costs likely will revolutionize how clinicians diagnose and treat diseases and enable the research community to pursue previously unimaginable scientific questions.

The Problem:

Even as we face the amazing and nearly innumerable scientific opportunities provided by this technological revolution, the development, testing, and delivery of new diagnostics and therapeutics remains a complex, costly, and risk-laden endeavor. In recent years, researchers have succeeded in identifying the causes of nearly 4,500 diseases, but we have been unable to turn this knowledge into many new therapies: effective treatments exist for only about 250 of these diseases. At the same time that we have all these therapeutic targets within our sights, only a few of the thousands of compounds that enter the drug development pipeline ultimately will make it into the medicine cabinet. It takes an average of 13 years at a cost of more than $1 billion to

bring a drug from target discovery to market. And along the way, more than 95 percent of potential therapeutics fail.[5][6][7]

To address this challenge, I proposed and the SMRB endorsed the creation of NCATS to address these frustrating bottlenecks in the therapeutic discovery pipeline. Working in collaboration, not competition, with the private sector, NCATS is designed to support rigorous scientific research aimed at reengineering elements of the drug development process and moving basic research findings into new treatments for patients more quickly and safely.

Teaching Old Drugs New Tricks:

On May 3rd, HHS Secretary Kathleen Sebelius and I announced the Discovering New Therapeutic Uses for Existing Molecules collaborative pilot program, in which compounds have undergone significant research and development by industry, including safety testing in humans, providing a head start or shortcut for scientists who want to test them for different therapeutic uses. This program aims to tackle an urgent need that is beyond the scope of any one agency, company, or non-profit. NCATS will manage the Therapeutic Discoveries program and match researchers with a selection of molecular compounds offered by companies to test their applicability for new therapeutic uses, with the ultimate goal of identifying promising new treatments for

[5] DiMasi, J.A, Hansen, R.W., Grabowski, H.G., "The price of innovation: new estimates of drug development costs." *Journal of Health Economics* 22 (2003) 151-185

[6] Collins, F.S., "Mining for therapeutic gold." Nature Reviews, Volume 10, page 397 (June 2011).

[7] Paul, S.M., Mytelka, D.S., Dunwiddle, C.T, Persinger, C.C, Munos, B.H., Lindbort, S.R., Schacht, A.L. "How to improve R&D productivity: the pharmaceutical industry's grant challenge." Nature, Volume 9, pages 203-214. (March 2010).

patients. As an example of what we're trying to do with this new initiative, consider that AZT once was a cancer drug but became an important therapy for AIDS patients, and Raloxifene was originally developed for osteoporosis but has become highly effective in treating breast cancer.

NCATS has partnered with Pfizer Inc., AstraZeneca, Eli Lilly and Company, Abbott, Bristol-Myers Squibb Company, GlaxoSmithKline, Janssen Pharmaceutical Research and Development L.L.C., and Sanofi. These eight companies have collectively agreed to make nearly 60 compounds available for the pilot program.

This is just one example of how NCATS will conduct and support research to develop enhanced methodologies and approaches in translational science that can be used by other NIH institutes and centers, academia, industry, and other sectors. Moreover, as NCATS advances our understanding of scientific targets and pathways, new avenues for scientific inquiry will be stimulated and pursued, ultimately reaffirming NIH's commitment to investing in basic science research.

V. U.S. Biomedical Research Leadership

NIH funding is the foundation for long-term U.S. global competitiveness in industries such as biotechnology, drug development, medical devices, and health care. So great is the return on our national investment in research, United for Medical Research and the Information Technology and Innovation Found reported that in 2011, a $1 billion investment in medical science is projected by economists to increase gross

domestic product by roughly $6 billion.[8] This same report stated that U.S. life sciences companies support more than 7 million jobs and account for $69 billion in U.S. economic activity.[9]

VI. Promise of NIH Research: Grand Challenges

Let me conclude my testimony by offering a few examples of where we see the greatest hope—and the greatest urgency—for more scientific investigation that leads to new understanding and new therapies.

Alzheimer's Disease:

As many as 5.1 million Americans currently suffer from Alzheimer's disease; more than 280,000 Americans will be diagnosed with the disease this year, with nearly 800 of our fellow citizens being diagnosed every day. By the year 2030, the last baby boomer will turn 65 and 7.7 million Americans over the age of 65 will have Alzheimer's disease.[10] Today, Alzheimer's and other dementias cost the U.S. economy more than $180 billion a year and if no cures and therapies are found, will cost the United States $1.1 trillion annually by 2050. Fortunately, new scientific advances have been showing remarkable promise, especially in the last few months.

Using mice genetically engineered to make the abnormal human *tau* protein—a protein already identified in the brains of Alzheimer's patients—scientists found that Alzheimer's disease appears to spread through the brain in much the same way that an infection moves through the body. The abnormal *tau* protein started in one area of the

[8] Atkinson, Robert, *et al.,* "Leadership in Decline: Assessing U.S. International Competitiveness in Biomedical Research." *Information Technology and Innovation Foundation and United for Medical Research* 5 (May 2010).
[9] *Id.* at 2.
[10] Alzheimer's Association, 2011 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, Volume 7, Issue 2

brain in the mice and, over time, spread from cell to cell to other areas of the brain in a pattern very similar to the earliest stages of human Alzheimer's disease. The discovery of the *tau* pathway could influence the direction of future research and give investigators a target for drug development that might arrest Alzheimer's disease progression at very early stages when the disease is most amenable to treatment.[11]

Alzheimer's disease also stands to benefit from translational research by way of drug rescuing and repurposing. Recently, a team that included NIH-supported investigators reported that bexarotene, a drug compound originally developed for treating T-cell lymphoma (a dangerous type of white blood cell cancer), was capable of clearing the protein beta-amyloid quickly and efficiently after only a short exposure to the compound in Alzheimer's disease mouse models. Beta-amyloid accumulates in the brain of Alzheimer's patients due to an impaired ability to clear the protein, leading to a build-up of beta-amyloid plaques and ultimately neuronal death. These findings are exciting because, in time, they could benefit patients with Alzheimer's disease. Researchers are especially hopeful because the drug used in the research has been studied already in humans, providing a wealth of information about dosage and toxicity.[12]

We are working to design additional non-invasive ways to detect the early brain changes characteristic of Alzheimer's disease. In the near term, we hope to develop drugs or other therapeutic strategies to delay the onset of Alzheimer's disease by a

[11] Liu L, Drouet V, Wu JW, Witter MP, Small SA, et al. (2012) Trans-Synaptic Spread of Tau Pathology In Vivo. PLoS ONE 7(2): e31302. doi:10.1371/journal.pone.0031302

[12] Cramer PE, Cirrito JR, Wesson DW, Lee CYD, Karlo JC, et al. (2012) ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models. http://www.sciencemag.org/content/early/2012/02/08/science.1217697.full.pdf

decade or more. And we are building new public-private partnerships to speed drug development by repositioning abandoned compounds.

Precision Medicine for Cancer:

Mutations in the genome of individual cells are what cause cancer, most often in response to something encountered in the environment, and cause good cells to go bad. Advances in DNA sequencing are now making it possible to identify the precise mutations that cause a normal cell to become malignant. The Cancer Genome Atlas is moving swiftly to sequence the tumor genomes of hundreds of cases of each of the twenty most prevalent forms of cancer. Such new knowledge is enabling us to discover new pathways and develop entirely new forms of targeted therapy. Soon, we may be able to apply this technology to allow every tumor in every cancer clinical trial to be sequenced within a few days of biopsy, allowing for a choice of the optimal therapy for each patient. Another opportunity we are pursuing is the development of new cancer biomarkers, including DNA circulating in the bloodstream, to identify responses to a given therapy. We hope to then use our knowledge of these responses to apply combination-targeted therapies and aim not only for response, but for cure.

Reverse the National Epidemic of Obesity:

The rising prevalence of obesity in the United States, especially in children, threatens to erase the gains in longevity achieved over the past decades. And, as I mentioned earlier, an increase in obesity brings an increase in its twin epidemic, diabetes.

To stem this epidemic, we are working to develop an evidence-based approach to helping people change their diets and personal habits. We also are exploring how to precisely define the molecular pathways that control weight. We hope to learn more about how diet and genetics interact at the level of the individual to increase the risk of diabetes and cardiovascular disease.

Secure an AIDS-free Generation:

In the past few years, NIH-supported researchers have learned that if people who are HIV-infected are diagnosed quickly and given HIV medications before they develop AIDS, the likelihood that they will transmit the virus to others is reduced by 96 percent.[13] This means that in the near future, a United States high school graduate might become part of the first AIDS-free generation in the country since the epidemic began. We also have the chance to build on recent advances to develop an effective vaccine against the human immunodeficiency virus itself, a goal that has frustrated us for thirty years.

Conclusion

Mr. Chairman and members of the Subcommittee, I offer these examples of the hope and promise that NIH research holds in part to thank you for your past support of NIH, but also to urge that you continue to invest in lifesaving biomedical research. NIH contributes to our economic growth and has secured our nation's leadership of the life sciences in the 21st century, but what motivates the scientific community has always

[13] Cohen, Myron S. et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. 2011. New England Journal of Medicine. 365: 493-505. doi:10.1056/NEJMoa1105243

remained the same: to apply the best science and medicine to end preventable human suffering from disease and disability.