DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2013

WEDNESDAY, MARCH 28, 2012

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 10 a.m., in room SD–124, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.

Present: Senators Harkin, Pryor, Mikulski, Brown, Shelby, Cochran, and Moran.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF FRANCIS S. COLLINS, M.D., Ph.D., DIRECTOR

ACCOMPANIED BY:

ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

GRIFFIN P. RODGERS, M.D., M.A.C.P., DIRECTOR, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE

RICHARD J. HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING

THOMAS R. INSEL, M.D., DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH, ACTING DIRECTOR, NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. The Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies will come to order.

Dr. Collins, welcome back to the subcommittee. Welcome also, Dr. Harold Varmus, Director of the National Cancer Institute (NCI); Dr. Tony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID); Dr. Griffin Rodgers, Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); Dr. Richard Hodes—again, good to see you again—Director of the National Institute on Aging (NIA); and Dr. Thomas Insel, both the Director of the National Institute of Mental Health and the Acting Director now of the new National Center for Advancing Translational Sciences (NCATS).

Again, my personal and professional thanks to all of you and the hundreds of thousands of people who are supported by National Institutes of Health (NIH) funding. Because of all of you, America is the world leader in biomedical research.

But how long America can maintain that status is a matter of growing concern. The threat of sequestration looms large. The Congressional Budget Office (CBO) has estimated that most nondefense discretionary programs, such as NIH, will be cut by about 7.8 percent next January if the Congress does not enact a plan before that time.

The budget plan proposed by the House Budget Committee chairman, which the House will vote on this week, is even more worrisome. In fiscal year 2013, the Ryan plan would cut nondefense spending by 5 percent. The following year, the plan will cut nondefense spending by 19 percent.

If that cut were applied equally across the Government, the number of new NIH grants for promising research projects would shrink by more than 1,600 in 2014 and by more than 16,000 during the next decade. That means 16,000 fewer opportunities to gain insights and possibly find cures for cancer and Alzheimer's and diabetes, and any number of other diseases.

Such a cut would be devastating not only for medical research but also for our economy. A study released last week by United for Medical Research concluded that, in 2011, NIH funding supported more than 430,000 jobs across the country. The link for this report follows: http://www.unitedformedicalresearch.com/wp-content/uploads/2012/07/NIHs-Role-in-Sustaining-the-US-Economy-2011.pdf.

Again, it always amazes me how most people think that all of that money goes to Bethesda, Maryland, and that is not so. Most is awarded to researchers at academic institutions all across the United States.

This same research also found that NIH research generated $62 billion in new economic activity last year. So now imagine cutting NIH funding by 19 percent in 2014.

Again, a classic case of pennywise and pound-foolish thinking, especially when China, India, and Europe are spending more, not less, on medical research.

But even under the best-case scenario, the budget for NIH is likely to remain tight for the immediate future, so we must do everything we can to ensure that NIH makes the most effective use of the money that is available.

That was part of the thinking behind the new NCATS, which this subcommittee created in last year's appropriations bill.

NCATS brings together, under one roof, translational activities that were already being funded but scattered throughout the NIH. For virtually no additional money, NIH now has an opportunity to address translational sciences in ways that we've never done before.

So, I look forward to hearing more about NCATS and other topics from our witnesses. And again, I just thank all of you for your great leadership of one of the great institutions of this country, the NIH.

And with that, I will yield to Senator Shelby for his opening statement.

STATEMENT OF SENATOR RICHARD C. SHELBY

Senator SHELBY. Thank you, Mr. Chairman.

I want to thank, at this time, Dr. Collins and the Center Directors who've joined us today to discuss the important role the NIH plays in every American's life.

For the millions of Americans suffering from a serious illness, biomedical research is the beginning of hope. NIH-funded research investigates ways to prevent disease, understand its causes, and develop more effective treatments.

A continued commitment to NIH is essential to addressing our Nation's growing health concerns and to spur medical innovation for the next generation of treatment and cures.

Unfortunately, the NIH budget request for the year 2013 abandons that commitment. The proposed budget for NIH is $30.86 billion, which is claimed to be level funding from fiscal year 2012. However, this amount does not take into account the additional funding the Department of Health and Human Services (HHS) requested for Departmentwide evaluation activities.

If this so-called evaluation tap is agreed to, it will reduce the NIH budget by $215 million, bringing the budget request below the 2012 level.

Further, the administration's request does not keep pace with biomedical research inflation, and as a result, in inflationary adjusted dollars, the NIH is 17 percent—that's right, 17 percent—below where they were 10 years ago.

Without sustained support for the NIH, the translation of discoveries from bench to bedside will be dramatically slowed, and the United States will surrender its role as a world leader in scientific research.

I do not agree with the funding level proposed by the administration for the NIH. I believe that the NIH funding should be a priority and that its benefits extend well beyond its research discoveries.

In 2011, NIH research funding supported 432,000 jobs nationwide. The research carried out by the NIH in this network of 325,000 researchers at 3,000 institutions across the country serves this Nation with the goal of improving human health.

However, Dr. Collins, I understand that your request attempts to live within the confines of a difficult budget environment. That said, I'm concerned about several of the proposed changes to awarding grant funding.

For example, you proposed capping the grant amount that a principle investigator can receive at $1.5 million. This proposal discourages success by limiting awards to some of the most successful scientists who accordingly receive the most grant funding.

NIH awards grants through a highly competitive, two-tiered, independent, peer-review process that ensures support of the most promising science and the most productive scientists. By limiting grant award amounts, you're changing the system from one that grants awards based on science, merit, and good ideas, to one based on whether an investigator has previously received a grant.

I'm also troubled with the proposals to cap inflationary cost and reduce the average award of competing research project grants below the fiscal year 2012 level. While I recognize that you're trying to keep your success rate high and fund as many grants as possible, I question whether this is the right approach. We do not want the only results of this change to be scientists spending more time chasing grants than making discoveries, and I don't believe you do either.

I understand that constrained budgets lead to tough decisions. However, it is critical that the NIH not lose sight of its goal to fund the best science in the hope of reducing the burden of illness.

A fundamental part of the NIH success over the years has been that scientific need and opportunity have always dictated NIH funding priorities.

Dr. Collins, I would caution you on opening the door to targeting particular diseases for funding as proposed in the fiscal year 2013 budget. The last thing I imagine you want is the President deciding what specific diseases deserve NIH research.

Finally, as we continue to operate in a tough budget environment, I think we need more out-of-the-box thinking to stimulate the research community in imaginative ways. In particular, I want to highlight such an approach at the NCI.

Dr. Varmus has started a new program to answer the provocative questions in cancer research. This project focuses scientists on 24 unanswered, perhaps nonobvious, questions as defined by the research community.

With more than 750 research teams submitting proposals, this project shows there are innovative ways to energize the research community, even when budgets are constrained.

And as the Congress faces unprecedented challenges to reduce Government spending, we must all face the consequences of tough choices. Certainly, these are difficult times, but I believe biomedical research is a necessary and worthy investment in the health of our people and the vitality of our communities.

PREPARED STATEMENTS

Funding for the NIH lays the foundation for drug and device discoveries over the next 10 years. Biomedical research is an answer to lowering, I believe, our Nation's healthcare costs. This is not the time to abandon our commitment to the health of all Americans and to the NIH.

PREPARED STATEMENT OF SENATOR RICHARD C. SHELBY

Thank you, Mr. Chairman. I want to thank Dr. Collins and the Center Directors who joined us today to discuss the important role the National Institutes of Health (NIH) plays in every American's life.

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Further, the administration's request does not keep pace with biomedical research inflation. As a result, in inflationary adjusted dollars, the NIH is 17 percent less than where they were 10 years ago. Without sustained support for the NIH, the translation of discoveries from "bench to bedside" will be dramatically slowed and the United States will surrender its role as the world leader in scientific research.

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That said, I am concerned about several of the proposed changes to awarding grant funding.

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I understand that constrained budgets lead to tough decisions. However, it is critical that the NIH not lose sight of its goal to fund the best science in the hope of reducing the burden of illness.

A fundamental part of the NIH's success over the years has been that scientific need and opportunity have always dictated NIH funding priorities. Dr. Collins, I caution you on opening the door to targeting particular diseases for funding as proposed in the fiscal year 2013 budget. The last thing I imagine you want is the President deciding what specific diseases deserve NIH research dollars.

Finally, as we continue to operate in a tough budget environment, I think we need more out-of-the-box thinking to stimulate the research community in imaginative ways. In particular, I want to highlight such an approach at the National Cancer Institute.

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As the Congress faces unprecedented challenges to reduce government spending, we must all face the consequences of tough choices.

Certainly these are difficult times, but I believe biomedical research is a necessary and worthy investment in the health of our people and the vitality of our communities.

Funding for the NIH lays the foundation for drug and device discoveries over the next decade. Biomedical research is the answer to lowering our Nation's healthcare costs. This is not the time to abandon our commitment to the health of all Americans and the NIH.

Senator SHELBY. Thank you, Mr. Chairman.

Senator HARKIN. Thank you very much, Senator Shelby.

Senator Inouye regrets that the could not be present but has a statement to be included in the record.

[The statement follows:]

PREPARED STATEMENT OF SENATOR DANIEL K. INOUYE

Mr. Chairman, thank you for chairing this hearing to review the President's fiscal year 2013 budget for the National Institutes of Health.

Mahalo (thank you), Dr. Collins, for joining us today. In this challenging fiscal environment, I will do my best to support the continued progress of science and U.S. competitiveness.

Senator HARKIN. Now we'll turn to Dr. Francis Collins, the 16th Director of the National Institutes of Health, a physician-geneticist noted for discoveries of disease genes and, of course, his leadership of the Human Genome Project.

Prior to becoming Director, he served as a Director of the National Human Genome Research Institute (NHGRI) at NIH.

Dr. Collins received his B.S. from the University of Virginia; M.D. from University of North Carolina at Chapel Hill; and Ph.D. from Yale University.

Dr. Collins, you're no stranger to this subcommittee. We welcome all of you here. Your statement of course, as usual, will be made part of the record in its entirety.

And I ask you to please proceed as you so desire. I won't put any clock time on it, so take whatever time you desire. If it starts going more than 10 minutes, however, we will get a little nervous, okay?

Welcome back. Please proceed.

SUMMARY STATEMENT OF DR. FRANCIS S. COLLINS

Dr. COLLINS. Thank you and good morning, Mr. Chairman and members of the subcommittee. I'm pleased to be here with my colleagues to present the President's budget request for the NIH for fiscal year 2013.

And I must begin by thanking you, Mr. Chairman, and the subcommittee members, for the ultimate fiscal year 2012 appropriation, which maintained NIH's budget at the fiscal year 2011 level. And we're also very grateful for your leadership in creating the new National Center for Advancing Translational Sciences (NCATS).

I do want to express my concern, since we're here in front of the subcommittee, about the health of Senator Kirk, and convey best wishes for a speedy recovery from all of us in the NIH community.

In the next few minutes, I want to offer some details associated with our budget request, to discuss the health and economic benefits of biomedical research, as you have done in your opening statements, and talk about the promise that lies at the intersection of the life sciences and technology.

As you can see here, and I'm going to show you some visuals, the President's fiscal year 2013 budget request for NIH is $30.86 billion, the same overall program level as in fiscal year 2012. This proposed appropriation will enable us to invest in areas with extraordinary promise for medical science.

We will also use these resources wisely to encourage a vigorous workforce prepared to tackle major scientific and health challenges.

As in the past, we will continue to support a wide array of research mechanisms, from investigator-initiated research to larger and more complex team and center efforts.

In fiscal year 2013, NIH expects to support an estimated 9,415 new and competing Research Project Grants (RPGs). That's an in-

crease of 672 more than the estimate for fiscal year 2012, with an average cost of about $431,000. For fiscal year 2013, total RPGs are expected to number around 35,888.

And also, to nurture early career scientists, we will continue our efforts to ensure that the success rates for investigators submitting new applications are the same, whether the applicant is first-time or more experienced.

To maximize funding for investigator-initiated grants and to continue our support of first-time researchers, we've had to make some tough choices.

For example, we propose to reduce budgets for noncompeting RPGs by 1 percent from the fiscal year 2012 level and to restrain growth in the average size of new awards. In addition, we will no longer assume out-year inflationary increases for new and continuing grants.

Other highlights of the fiscal year 2013 request include a $40 million ramp up of the Cures Acceleration Network (CAN) and additional support for Alzheimer's disease research, $80 million coming as part of an HHS-wide initiative.

NIH-funded research has prevented untold human suffering by enabling Americans to live longer, healthier, and more productive lives, and let me mention a few examples.

Life expectancy: A child born today can look forward to an average lifespan of almost 79 years. That's nearly three decades longer than one born in 1900.

Cardiovascular disease: During the last half-century, our Nation's death rates for heart disease and stroke have fallen by 70 percent.

Infant mortality: We've achieved an impressive 40-percent reduction in this vital area over the last two decades.

In cancer, the just released 2012 annual report to the Nation on the status of cancer shows a continuing decline in death rates for most cancers, along with a drop in the overall rate of new cancer diagnoses.

And today's biomedical research holds much, much more promise. For example, I want to show you this picture of a recent publication of research on Alzheimer's disease, and this represents a new opportunity in translational research through what we would call drug repurposing.

Recently, a team of researchers, some supported by NIH, found that a drug called bexarotene, a drug originally developed for treating a type of skin cancer, can clear beta-amyloid, as you see in the before and after picture, in mouse models of Alzheimer's disease in just 72 hours.

In people with Alzheimer's, beta-amyloid accumulates in the brain like this, eventually leading to the death of neurons. Hope for bexarotene has gone particularly high because it has already been studied in humans, providing a wealth of information about dose and toxicity, and providing the opportunity to initiate clinical trials.

And that's not all. Here's a list, Senator and members of the subcommittee, of just a few of the many recent examples of progress in biomedical research, scrolling by here. I wish I could tell you the

details of each one, but this opening statement would then go on for most of the day.

I would like, however, to talk something about the U.S. economy, as you have touched on, both of you, in your opening statements.

As our Nation struggles to recover from a difficult period, it's worth pointing out that Government investments in biomedical research are a terrific way to spur economic growth. A recent analysis estimated that every $1 of NIH support returns $2.21 in goods and services to the local economy in just 1 year. And on average, every NIH grant creates seven high-quality jobs.

Furthermore, NIH serves as the foundation for the entire U.S. medical innovation sector, a sector that employs 1.42 million directly and supports an additional 6.6 million jobs in the United States, resulting in a total employment impact of more than 8 million jobs, generating $84 billion in wages and salaries, and exporting $90 billion in goods and services.

Already referred to, the latest figures from the United for Medical Research report paint a similar picture. According to their update, NIH recently, directly and indirectly, supported more than 432,000 American jobs, spurring more than $62 billion in economic activity.

And here's another thing to consider: NIH funding is the foundation for long-term U.S. global competitiveness in industries such as biotech, drug development, and medical devices. Around the world, many nations are following America's success story and ramping up their investments in the life sciences.

Global research and development (R&D) spending across the world is expected to grow by about 5.2 percent to more than $1.4 trillion in 2012. India has posted double-digit percentage increases in R&D for several years. Europe plans to increase research spending by 40 percent over the next 7 years. China has just announced that it will increase its investment in basic research by 26 percent in 2012. And Vladimir Putin has voiced his intention to increase support for research in Russia by 65 percent during the next 5 years.

Let me now turn to a few areas that are driving medical research. No less a futurist than Steve Jobs once predicted, "I think the biggest innovations of the 21st century will be the intersection of biology and technology." And he was spot on.

One striking example is the cost of sequencing a human genome. Eleven years ago, it cost $100 million. Five years ago, $10 million. Today, less than $8,000 and heading down.

Within the next year or two, in fact, a couple of U.S. companies plan to sell machines that can sequence a genome in a single day for $1,000 or less, using devices like the one I'm holding up here, the size of a postage stamp. That's a sequencing machine. It used to be as big as a phone booth or bigger. This is a new model.

This will revolutionize how doctors diagnose and treat diseases and will allow researchers to pursue previously unimaginable scientific questions.

So this kind of advance in technology empowers both basic and applied research, and NIH is a leading supporter of basic biomedical research in the world.

Slightly more than one-half of NIH's budget is being invested to support this kind of fundamental research. In our view, there is no competition between basic and applied research. They're synergistic. And our support of basic research makes possible a wide range of new biological discoveries.

Take the example of induced pluripotent stem cells, stem cells derived from patients' own skill cells. This technology is now being used to develop exciting new models of disease, so-called "diseases in a dish," that are expanding our understanding of human biology, as well as opening the door to new treatment possibilities.

But let's be honest. There's much work yet to be done. Despite phenomenal progress in basic science, we still lack effective treatments for far too many diseases.

And the translational pipeline is long; 14 years on the average. And it's terribly leaky.

A recent article in the Journal Nature Reviews Drug Discovery found that despite huge R&D investments, the number of new drugs approved per $1 billion, as you see here, has fallen steadily since 1950. Bottlenecks continue to vex this process, resulting in long development times, high failure rates, and steep costs.

We need to re-engineer this pipeline, and that's why our new center, NCATS, is already working with industry to develop innovative ways to speed the flow of new therapies to patients.

Mr. Chairman, I've described the administration's fiscal year 2013 request for NIH, the health and economic benefits of biomedical research, and the synergy between basic and translational research at NIH that's made possible by today's technological advances. But I'd like to close with a story that ties these points together.

As toddlers, the twins Alexis and Noah Beery were diagnosed with a rare and devastating movement disorder called dystonia. Although they initially responded to standard treatment, their symptoms reappeared and worsened.

Noah developed severe tremors in his hands. And Alexis encountered even greater difficulties. As you can see in this heartbreaking video clip, she began falling frequently and had frightening episodes where she could not breathe.

Desperate for answers, doctors at Baylor College of Medicine sequenced the twins' genomes. The result was the discovery of a never-before described genetic mutation affecting neurotransmitters in the brain. After being put on a new treatment regimen tailored to their unique genetic profile, the twins' symptoms began to improve within just 2 weeks.

In fact, Alexis' breathing is so much better today that she has joined the school's track team.

Tonight in a NOVA special on advances in genetic medicine, PBS viewers will be able to witness the twins' progress. And here's a sneak peak. That's Noah and Alexis, healthy, happy, and enjoying themselves on a trampoline.

PREPARED STATEMENTS

While this study centers on teens with a rare disease, the outcome carries a message of hope for all of us. It points directly to

the promise that NIH research offers the patients of today and tomorrow.

So thank you for this opportunity, Mr. Chairman and members of the subcommittee. And my colleagues and I will be glad to answer your questions.

[The statements follow:]

PREPARED STATEMENT OF FRANCIS S. COLLINS, M.D., PH.D.

NATIONAL INSTITUTES OF HEALTH'S MISSION

Good morning, Mr. Chairman and distinguished members of the subcommittee. I am Francis S. Collins, M.D., Ph.D., and I am the Director of the National Institutes of Health (NIH). I have with me Anthony S. Fauci, M.D., Director of the National Institute of Allergy and Infectious Disease (NIAID); Richard J. Hodes, M.D., Director of the National Institute on Aging (NIA); Thomas R. Insel, M.D., Director of the National Institute of Mental Health (NIMH), and the Acting Director of the new National Center for Advancing Translational Sciences (NCATS); Griffin P. Rodgers, M.D., Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); and Harold E. Varmus, M.D., Director of the National Cancer Institute (NCI).

It is a great honor to appear before you today to present the administration's fiscal year 2013 budget request for the NIH.

First, I would like to 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. In particular, I want to thank the subcommittee for your support during the fiscal year 2012 appropriations process, for the ultimate appropriation of $30.62 billion for NIH, and for the provisions that established NCATS.

As the largest supporter of biomedical research in the world, NIH has been a driving force behind decades of advances that have improved the health of people across the United States and around the world.

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

—nearly 70-percent reduction in the death rate for coronary disease and stroke in the last half century;
—effective interventions for HIV/AIDS prevention and treatment, such that an AIDS-free generation may be within our grasp;
—nearly 30-percent decline during the last three decades in the age-standardized prevalence of chronic disability among American seniors;
—40-percent decline in infant mortality during 20 years and better treatments for premature and low-weight births that result in increased infant survival, the prevention of cerebral palsy, and better developmental outcomes; and
—more than 150 U.S. Food and Drug Administration (FDA)-approved drugs and vaccines, or new uses of existing drugs.[1]

The administration's fiscal year 2013 budget request for NIH is $30.86 billion, which is the same overall program level as fiscal year 2012. This proposed appropriation will enable us to spark innovation and invest in areas of extraordinary promise for medical science. We will also invest these resources wisely to encourage a vigorous workforce that is prepared to tackle major scientific and health challenges.

Within the administration's fiscal year 2013 budget, we will continue to protect and increase Research Project Grants (RPGs), NIH's fundamental funding mechanism for investigator-initiated research. NIH expects to support an estimated 9,415 new and competing RPGs in fiscal year 2013, an increase of 672 more than the estimate for fiscal year 2012, with an average cost of about $431,000. For fiscal year 2013, total RPGs are expected to number around 35,888.

To maximize funding for investigator-initiated grants, and to continue our support of first-time researchers, we propose to reduce budgets for noncompeting RPGs by 1 percent from the fiscal year 2012 level and to restrain growth in the average size of new awards. We will also no longer assume out-year inflationary increases for

[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.

new and continuing grants. To nurture early career scientists, we will continue our efforts to ensure that the success rates for investigators submitting new R01 applications are the same whether the applicant is first-time or more experienced.

In fiscal year 2013, we will also conduct an additional review of proposed awards to any principal investigator (PI) who already has NIH funding of $1.5 million or more in total annual costs, approximately 6 percent of PIs. This review will be conducted by each institute's advisory council. This is similar to a policy the National Institute of General Medical Sciences (NIGMS) has had since 1998, which will serve as a model for NIH. We recognize that some types of research, notably large complex clinical trials, routinely will trigger this review. We also know that some of our most productive investigators are leading significant research teams that require more than $1.5 million to be sustained. This extra level of review will not be viewed as a cut-off point but as an opportunity to apply additional scrutiny to be sure any added resources are justified by exceptional scientific promise.

Another significant change in the fiscal year 2013 request is an 11-percent increase in the NCATS budget. The proposed budget includes an increase of $39.6 million for the Cures Acceleration Network (CAN), which received $10 million for start-up funding in fiscal year 2012. As you know, Mr. Chairman, CAN will fund initiatives to address scientific and technical challenges that impede translational research, and to advance the development of "high-need cures" by accelerating the pace and reducing the time between research discovery and therapeutic treatment. In total, nearly one-half of the increase requested for NCATS will be used to transition programs from the Common Fund, allowing the Common Fund to support additional cross-cutting, trans-NIH programs.

I would also note that the fiscal year 2013 NIGMS budget would decrease by $48.3 million (after comparability adjustments), primarily due to not continuing the 21 percent increase that the Congress provided in fiscal year 2012 for the Institutional Development Awards (IDeA) program. The budget of the Office of the Director is also cut by 1.9 percent from fiscal year 2012 enacted level, reflecting a reduced request for the National Children's Study (NCS); we will implement alternative sampling approaches that will reduce costs and still achieve the ambitious objectives of the study.

In fiscal year 2013, the President is also proposing to spend $80 million from the Prevention and Public Health Fund to provide additional support for Alzheimer's research as part of the national plan to address Alzheimer's disease. As many as 5.1 million Americans currently suffer from Alzheimer's disease, more than 280,000 more Americans will be diagnosed with the disease this year, and nearly 800 of our fellow citizens are diagnosed every day. By the year 2030, the last baby boomer will turn 65 and 7.7 million Americans older than the age of 65 will have Alzheimer's disease.[2] Today, Alzheimer's and other dementias cost the United States 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. The $80 million of new funding will support research with a strong focus on the prevention of Alzheimer's disease, including research to identify genes that cause this disease, to develop tests for high-risk individuals, and to identify possible targets for therapeutic development.

INVESTING IN BASIC SCIENCE, APPLYING KNOWLEDGE TO THERAPIES

NIH's commitment to basic research provides the foundation for understanding the underlying causes of diseases which is essential to the development of promising treatments and cures for some of our Nation's most debilitating diseases and conditions. Apple Computer founder, Steve Jobs, has been quoted as saying: "I think the biggest innovations of the 21st century will be the intersection of biology and technology."[3] Jobs was absolutely right: 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 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 5 years ago, to about $7,700 today. Two U.S. companies have recently announced that they are manufacturing machines that will sequence an individual's genome in 1 day for approximately $1,000, and that the first such instruments will go on sale before year's end. Lower sequencing costs will likely revolutionize how clinicians diagnose and treat diseases and enable the research community to pursue previously unimaginable scientific questions.

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[2] Alzheimer's Association, 2011 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, Volume 7, Issue 2.

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

NIH is the leading supporter of basic biomedical research in the world. Put plainly, if we don't fund basic research, most of this work would not get done, and it would be only a matter of time before this wellspring of new understanding and new therapies would dry up. NIH's funding for basic research is slightly more than one-half (54 percent) of research funding, and this balance between basic and applied research has remained fairly constant over the past decade.

I also would like to address what may be a misconception about a competitive tension between basic and applied research at NIH. As our support of basic research has enabled new discoveries, NIH-funded scientists have always worked to turn the most compelling of them into medical advances. Basic discovery and the development of therapies go hand-in-hand at NIH. The two types of research have—and always will—exist together in a continuum. Today, I would like to highlight just a few areas in which basic research advances are opening up new translational opportunities.

Human Microbiome Project.—One fascinating area of basic research is the Human Microbiome Project, an initiative supported through the NIH common fund. This project is giving us wonderful insights into the sweeping range of bacteria that live on and in each of us, and is expanding our knowledge about the role of these microbial communities in health and disease. Recent scientific evidence suggests that changes in the composition and activity of the human microbiome may contribute to obesity, which may provide us with new ways of addressing this serious threat to our Nation's health.

Undiagnosed Diseases Program.—Another recent example emphasizes the "virtuous cycle" between basic and clinical research. The NIH clinical center has recently established a groundbreaking program that seeks to identify the cause of illnesses that have remained unsolved by other medical practitioners. Since the program started in 2008 some 1,700 people with undiagnosed conditions have been referred to Dr. William Gahl, and more than 300 have been accepted for an initial week of consultations and testing. In the 15 to 20 percent of cases that we have successfully diagnosed, it has taken from a week to as long as 2 years to resolve. For example, a pair of sisters from Kentucky suffered from joint pain and mysterious calcification of the arteries in their extremities. Full evaluation and DNA sequencing led to the discovery of an entirely new genetic condition, where a previously unknown enzyme pathway in their arteries was blocked. This has led to a dramatic new understanding of how the large arteries in all of us maintain their normal health, with immediate research spinoffs in the basic and clinical arenas.

Alzheimer's Disease.—NIH-supported investigators are expanding our understanding of Alzheimer's disease in ways that may open doors to new therapies. 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 or cancer moves through the body. The abnormal tau protein started in one area of the 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.[4]

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 type of skin 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. Hopes are particularly high because the drug used in the study has already been studied in humans, providing a wealth of information about dosage and toxicity.[5]

Cystic Fibrosis.—In a step towards personal medicine, the FDA in January approved Kalydeco, the first drug to treat an underlying cause of cystic fibrosis (CF). Twenty-three years ago, I co-led the team that discovered the gene responsible for

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[4] 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

[5] 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

CF. Mutations in this gene cause a protein to malfunction, resulting in a sticky buildup of mucus in the lungs and digestive tract that eventually causes fatal health problems. Kalydeco, which was developed by Vertex Pharmaceuticals, counters one of these mutations, which affects about 4 percent of people with CF. Vertex is now testing the drug in combination with another new compound to target a more common mutation found in 90 percent of CF patients.

CLINICAL RESEARCH: NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

The translation of basic biological discoveries into clinical applications is a complex process that involves a series of intricate steps. These steps range from the discovery of basic information about the causes of disease, an assessment of whether that information has the potential to lead to a clinical advance, the development and optimization of therapeutics to test in human trials, and ultimately, the application of the approved therapy, device, or diagnostic in the real world. Drugs exist for only about 250 of the more than 4,400 conditions with defined molecular causes.[6] And it takes far too long and far too much money to get a new drug into our medicine cabinets. This is an old problem that cries out for new and creative solutions.

In the past, drug development was based on a short list of a few hundred targets, but with advances in technology, we are now able to identify thousands of new potential drug targets.[7] We can also study whole pathways, organ systems, or even entire organisms rather than limiting the research to a single aspect of cell biology or physiology. Technologies such as large-scale sequencing, robotic high-throughput screening, and real-time imaging modalities uncover massive amounts of data that may one day lead to new therapies to prevent, treat, and possibly cure diseases. Many of the NIH institutes are deeply engaged in these efforts. But we face serious engineering challenges. To put it simply, the current translational science framework pursued in both the public and private sectors, largely focused on individual projects on specific diseases, has not been fully able to utilize recent scientific advances to address the bottlenecks that lead to long development times, high failure rates, and high costs. This month's issue of Nature Reviews Drug Discovery includes a review that demonstrates that, despite huge investments in biomedical science and technology, the number of new drugs approved per billion R&D dollars spent has been cut in one-half every 9 years since 1950.[8] NCATS is the catalyst we need to reengineer the discovery and development process.

To tackle this problem in a science-driven way, NIH proposed the creation of NCATS with the goal to develop and test innovative tools, technologies, and approaches that will enhance the development of drugs and diagnostics for application in all human diseases. NIH has the expertise and enthusiasm to tackle this as a scientific problem. By focusing on the development of innovative new methods for conducting translational science, as opposed to developing therapeutics themselves, NCATS can enable others to bring new medical products to patients in a highly efficient, cost-effective manner. In the 4 months since it was established, NCATS has already developed three new initiatives in partnership with industry, academia, and other government agencies.

In the first initiative, NIH is working closely with several pharmaceutical companies to develop model agreements for a new pilot program to rescue failed drugs. Pharmaceutical companies have access to promising compounds that have been shown to be safe in humans, but that did not prove effective in treating the condition for which they were intended. Researchers are now learning that a compound that is a failure for one condition may help to treat another. To capitalize on this, NCATS is developing a pilot program in partnership with industry that will seek to crowd source some of the most promising of these compounds to the brightest minds in science, an unprecedented opportunity for NIH-funded researchers, and a new way to bridge academic science with industrial expertise.

Second, NCATS is partnering with the Defense Advanced Research Projects Agency (DARPA) to develop a chip that will mimic how humans respond to a drug. Scientists funded by NIH and DARPA will spend 5 years working closely with each other to place 10 diverse human tissues on a chip so that they will interact with drugs the same way that they do in living patients. By providing a better model

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[6] Braun, et al., "Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years." Nature Rev. Drug Discov. 9(521), 2010; Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/omim/.

[7] Collins, F.S., "Reengineering Translational Science: The Time is Right." Sci. Transl. Med., 3(90):90cm17, 2011.

[8] Scannell JW, Blanckley A, Boldon H, & Warrington B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. Nature Reviews Drug Discovery 11, 191-200. doi:10.1038/nrd3681.

to predict drug safety and efficacy, the most promising drug candidates can be identified more quickly and moved forward into development. FDA will be heavily involved in an advisory capacity to ensure this research aligns with regulatory requirements.

In the third initiative, NCATS is working closely with industry to develop systematic ways to identify the most promising drug targets from the troves of data pouring out of basic research labs. To turn these discoveries into therapies, scientists in academia and industry need to be able to sift quickly and accurately through these data to identify the best targets. NCATS, along with industry partners, is taking the lead on developing a consortium that will strive to come up with the most streamlined ways to conduct target validation.

I want to emphasize that these and other initiatives within NCATS will provide resources and expertise to assist the basic research community in moving their discoveries to the next phase, as well as stimulate the basic research enterprise. For example, the Molecular Libraries and Imaging Program, originally implemented through the NIH Common Fund, has been successful in the development of chemical probes for basic and translational research. Many of these new probes have been, or are being, modified for use in the clinic, resulting in patent applications, licenses to pharmaceutical companies, and new therapeutic strategies.

In the months before NCATS was created by this subcommittee, NIH engaged in an unprecedented outreach campaign to make sure that all stakeholders—including industry—had an opportunity to comment on the proposed Center. In addition to NIH's scientific management review board and advisory council to the director, NIH consulted with the boards of the Pharmaceutical Research and Manufacturers of America and the Biotechnology Industry Association, the R&D heads of pharmaceutical and biotechnology companies, and the investment banking and venture capital communities. In addition, NIH held a series of workshops with pharmaceutical and biotech firms to discuss drug rescue and repurposing and target validation.

It is important to note that NCATS' work will assist all of NIH's Institutes and Centers in their translational and drug development efforts. NCATS will provide NIH Institutes and Centers the tools, methodology, and infrastructure necessary to speed new approaches to therapeutic treatments. The new Center also will work with other NIH Institutes and Centers to convene workshops with industry, nonprofits, and other government agencies to explore critical translational areas and innovative public-private sector partnerships.

With the fiscal year 2013 budget, NIH will pursue efforts to streamline and shorten the pathway from discovery to health through several new and ongoing initiatives and programs.

ECONOMIC RETURNS AND GLOBAL COMPETITIVENESS

In our knowledge-based world economy, innovation in medical research has been able to generate growth, high-quality jobs, better health, and better quality of life for all Americans. Investment in NIH continues to bring new ways to cure disease, alleviate suffering, and prevent illness. Furthermore, it generates new economic activity and employment in the communities that receive its funds. One study estimates that every $1 of NIH support returns $2.21 in goods and services in just 1 year, and that on average, every NIH grant creates seven high-quality jobs.

Investments in the biomedical infrastructure, in scientists' ideas, and in workforce training are essential to drive the innovation that will spur America's economic recovery and future growth. NIH serves as the foundation for the entire U.S. medical innovation sector that employs 1 million United States citizens, generates $84 billion in wages and salaries, and exports $90 billion in goods and services.[9] United for Medical Research has just released an updated version of their report "An Economic Engine: NIH Research, Employment, and the Future of the Medical Innovation Sector." According to UMR data, the $23.7 billion NIH spent extramurally in the U.S. in 2011 directly and indirectly supported 432,092 jobs, enabling 16 States to experience job growth of 10,000 jobs or more, and propelling $62.135 billion in new economic activity.

Thanks in large part to NIH-funded medical research, Americans are living longer, healthier, more rewarding lives. A child born today can look forward to an average life span of almost 79 years, an increase of nearly three decades over life expectancy in 1900. The economic value of these gains in average life expectancy

[9] Ehrlich, Dr. Everett, An Economic Engine: NIH Research, Employment and the Future of the Medical Innovation Sector, 8, United for Medical Research (May 2011).

in the United States has been estimated at $95 trillion for the period from 1970–2000.[10]

NIH funding is the foundation for long-term U.S. global competitiveness in industries such as biotechnology, medical devices, and pharmaceutical development. Around the world, many nations are following suit and beginning to ramp up their own investment in the life sciences. Global R&D spending is expected to grow by about 5.2 percent to more than $1.4 trillion in 2012.[11] India has posted double-digit increases for several years, and Europe plans to increase research spending by 40 percent over the next 7 years. Even Vladimir Putin has announced the intention to increase support for research in Russia by 65 percent over the next 5 years. China has just announced that it will increase its investment in basic research by 26 percent in 2012.[12] To be sure, the scale of China's effort does not match ours. However, Chinese scientists are second only to the United States in the number of scientific manuscripts published annually, and China's intention to compete with us is obvious.

The United States must compete in training America's next generation to make tomorrow's health discoveries and ensure continued scientific leadership.

A PATIENT STORY

Mr. Chairman, this morning I've described the promise that inexpensive whole-genome sequencing holds for future medical practice, the synergy between basic and translational research at NIH, and the need for NCATS. I'd like to close my testimony by telling you a story—a story about real patients—that ties my three points together.

As toddlers, twins Alexis and Noah Beery were diagnosed with a rare and devastating movement disorder, called dystonia. Although they initially responded to empirical treatment, their symptoms reappeared and worsened as they entered their teenage years. Noah developed severe tremors in his hands. Even worse, his sister Alexis began falling frequently and had frightening episodes where she couldn't breathe.

Desperate for answers, doctors at Baylor College of Medicine sequenced the twins' genomes. The result? Discovery of a never-before described genetic mutation affecting neurotransmitters in the brain. After being put on a new treatment regimen tailored to their unique genetic profile, the twins' symptoms began to improve within just 2 weeks. I recently saw a video of the two of them doing tricks on a trampoline. In fact, Alexis' breathing is so much better today that she's joined her school's track team. While this story centers on two teens with a rare disease, the outcome carries a message of hope for all of us. It points directly to the promise that NIH research offers the patients of today and tomorrow.[13]

In conclusion, we have never witnessed a time of greater promise for advances in medicine than right now. NIH is prepared to continue our long tradition of leading the world in the public support of biomedical research. Successful development of prevention strategies, diagnostics, and therapeutics will require bold investments in research across the spectrum from basic science to clinical trials, as well as new partnerships between the public and private sectors. With your support, we can promise continuing advances in medicine, creation of new economic opportunities, and stimulation of American global competitiveness in science, technology, and innovation.

PREPARED STATEMENT OF ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Mr. Chairman and members of the subcommittee: I am pleased to present the President's fiscal year 2013 budget request for the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The fiscal year 2013 NIAID budget of $4,495,307,000 includes an increase of $10,210,000 more than the comparable fiscal year 2012 level of $4,485,097,000.

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[10] Murphy, K.M., & Topel, R.H. (2006). "The value of health and longevity". Journal of Political Economy, 114(5), 871-904.

[11] Grueber, Martin, 2012 Global R&D Funding Forecast, 3, Batelle and R&D Magazine (December 2011).

[12] Hvistendahl M. (2012). "A Bumper Year for Chinese Science." Science Vol. 335, No. 6073 p.1156. doi: 10.1126/science.335.6073.1156.

[13] Bainbridge MN, et al. (2011). Whole-Genome Sequencing for Optimized Patient Management. Science Translational Medicine 3, 87re3. doi: 10.1126/scitranslmed.3002243.

NIAID conducts and supports biomedical research to understand, treat, and prevent infectious and immune-mediated diseases, including HIV/AIDS, tuberculosis, malaria, influenza, emerging and re-emerging infectious diseases, asthma and allergic diseases, autoimmune diseases, and the rejection of transplanted organs. I appreciate the opportunity to highlight our recent scientific advances and to describe some of our most promising research aimed at improving public health and quality of life.

INFECTIOUS DISEASES RESEARCH

HIV/AIDS.—In the 30 years since AIDS was first recognized in the United States, the substantial NIAID investment in basic, translational, and clinical HIV/AIDS research supported consistently by this subcommittee has resulted in many groundbreaking discoveries. With this commitment, we have made significant progress, including strengthening HIV prevention efforts and developing nearly 30 antiretroviral drugs to suppress HIV. Thirty years ago, HIV/AIDS was for the most part a death sentence. Today, if a young person enters the clinic with early HIV disease and begins appropriate therapy, he or she can expect to live a near-normal lifespan, a milestone unimaginable at the start of the HIV/AIDS pandemic.

I am pleased to report landmark advances and opportunities in HIV/AIDS research this year. In December 2011, the journal Science named an NIAID-funded international HIV prevention study its breakthrough of the year, reinforcing that the investment in NIH research continues to pay extraordinary dividends for public health. This study, known as HPTN 052, demonstrated that HIV-infected heterosexual individuals who began taking antiretroviral medicines when their immune systems were still relatively healthy, rather than later, were 96 percent less likely to transmit the virus to their uninfected sexual partners. This study convincingly demonstrates that antiretrovirals not only can be life-saving to people infected with HIV but also can prevent transmission of the virus to their uninfected sexual partners. Other studies have shown that medically supervised adult male circumcision has proven to be highly effective and durable in preventing the acquisition of HIV infection. In addition, pre-exposure prophylaxis of at-risk uninfected individuals may be an important means of preventing HIV infection.

HIV vaccines still represent the best long-term hope for ending the HIV pandemic. Building on the promising results of the United States Army-NIAID RV144 HIV vaccine clinical trial, which found a "prime-boost" vaccine candidate to be safe and modestly effective at preventing acquisition of HIV, NIAID is working to understand the immune mechanisms that explain these results, to optimize the protective immune responses elicited by the vaccine candidate, and to develop and evaluate new vaccine candidates. We also are encouraged by the discovery by NIAID-supported scientists of human antibodies that can block a wide range of HIV strains. We are expanding clinical testing in this area, and insights gained from these studies will guide future HIV vaccine research.

These research advances taken together with the implementation of other evidence-based HIV prevention and treatment strategies make the possibility of an "AIDS-free generation" in the foreseeable future eminently feasible. This July, we will consider strategies to implement these important findings during the International AIDS Society Conference in Washington, DC.

Tuberculosis and Malaria.—NIAID continues to invest in basic and clinical research and collaborate with global partners, including the World Health Organization's Stop Tuberculosis (TB) Partnership, to combat the co-infections that often accompany HIV infection, including TB and malaria. Building on these efforts, we now have a substantial development pipeline of TB treatments and vaccines. NIAID has developed a Strategic Blueprint for TB Vaccines that proposes new research pathways for achieving a licensed TB vaccine. For malaria, NIAID supported early-stage basic research that ultimately led to the development by others of the first moderately successful malaria vaccine candidate aimed particularly for children, RTS,S/AS01, a science runner-up breakthrough of the year in 2011. In addition, the NIAID Vaccine Research Center is partnering with a biotechnology firm to undertake clinical studies of a novel malaria vaccine candidate, PfSPZ. NIAID also plays a leading role in the international Malaria Eradication Research Agenda initiative.

Other Infectious Diseases of Domestic and Global Health Importance.—NIAID's longstanding investments in basic and clinical research have led to many successes in vaccine development for diseases of worldwide public health concern, including gastroenteritis caused by rotavirus, pneumonia, hepatitis A, and deadly meningitis caused by Haemophilus influenzae type b. These are among the vaccines now being delivered to countries around the world; where they have been deployed, substantial reductions in morbidity and mortality have been observed. NIAID has assumed a

major leadership role in the "Decade of Vaccines" initiative, a 10-year collaborative effort coordinated by the Bill & Melinda Gates Foundation, to develop and deliver vaccines to the world's poorest countries. NIAID will continue research on other urgently needed vaccines, including vaccines for Group B streptococci, Epstein-Barr virus, and hepatitis C virus.

Seasonal and pandemic influenzas remain critical global health and economic threats. NIAID has made significant progress in the development and testing of vaccines to protect people from influenza, including the elderly, young children, and those with asthma. Recently, NIAID researchers demonstrated that a "prime-boost" gene-based vaccination strategy could activate the immune system and lead to broadly neutralizing antibody responses against influenza viruses. This finding and those from other researchers signal that we are closer to developing a "universal" vaccine that could protect against multiple strains of seasonal and pandemic influenza viruses.

This year, in response to the growing public health issue of antimicrobial resistance, NIAID will expand our clinical trials networks developed originally for HIV/AIDS to investigate this important concern. In addition, NIAID will support research to determine how to preserve the effectiveness of current antibiotics.

NIAID's biodefense research has yielded numerous scientific advances as we have moved from a "one bug-one drug" approach to a more flexible, broad-based product development strategy that utilizes sophisticated genomic and proteomic platforms to address infectious disease outbreaks, whether they are deliberately introduced or naturally occurring. As part of this effort, NIAID has awarded contracts for the development of broad-spectrum therapeutics against emerging infectious disease and biodefense agents.

RESEARCH ON IMMUNOLOGY AND IMMUNE-MEDIATED DISORDERS

NIAID was highly gratified that the 2011 Nobel Prize in Physiology or Medicine was awarded to three NIAID grantees:

—Bruce A. Beutler;

—Jules A. Hoffmann; and

—the late Ralph M. Steinman.

Their research has been pivotal in understanding the human immune response, and it is helping to inform the development of new vaccines and vaccine adjuvants that may provide better protection against infectious diseases.

NIAID's commitment to basic immunology research has led to advances in the treatment of immunological conditions such as the rejection of transplanted organs. In 2011, the Journal of the American Medical Association published an NIAID Immune Tolerance Network study demonstrating that children who receive liver transplants may not need lifelong anti-rejection therapy to maintain the transplanted organ. Other NIAID-supported investigators demonstrated that some kidney transplant recipients who also received bone marrow from the kidney donor can maintain their kidney grafts without immunosuppressive drugs.

CONCLUSION

NIAID basic and clinical research on infectious and immune-mediated diseases will continue to promote the development of vaccines, therapeutics, and diagnostics to improve health and save millions of lives worldwide. NIAID remains committed to supporting highly meritorious research with the goal of translating fundamental scientific findings into public health advances.

PREPARED STATEMENT OF GRIFFIN P. RODGERS, M.D., M.A.C.P., DIRECTOR, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Mr. Chairman and members of the subcommittee: I am pleased to present the President's fiscal year 2013 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The fiscal year 2013 budget includes $1,792,107,000, which is $2,798,000 less than the comparable fiscal year 2012 appropriation of $1,794,905,000. Complementing these funds is an additional $150 million also available in fiscal year 2013 from the special statutory funding program for type 1 diabetes research. The NIDDK supports research on a wide range of common, chronic, costly, and consequential diseases and health problems that affect millions of Americans. These include diabetes and other endocrine and metabolic diseases; digestive and liver diseases; kidney and urologic diseases; blood diseases; obesity; and nutrition disorders.

BUILDING NEW OPPORTUNITIES: BASIC RESEARCH DISCOVERIES

From in-depth exploration of fundamental biologic processes, NIDDK-supported scientists are achieving remarkable advances and building the foundation for previously unimaginable strategies to improve health and quality of life. Among these advances, recent NIDDK-supported research into genetic risk factors for diabetes, inflammatory bowel disease, obesity, liver disease, and the kidney disease focal segmental glomerular sclerosis, along with other studies are providing insights into disease development and whether an individual is likely to respond to a given therapy. Investigating the different types of bacteria that reside in the intestines, researchers have discovered surprising links to obesity, inflammatory bowel disease, fatty liver disease, and other health conditions. Scientists supported by our institute are also designing novel intervention strategies and testing these in pre-clinical, laboratory models. For example, pursuing a treatment for fecal incontinence, researchers used tissue engineering to build muscle implants in mice with promising initial results, providing hope for future therapeutic use in people. Other scientists examined a potential drug for the rare disease Neimann-Pick type C in experiments with isolated human cells, and found encouraging results.

We will continue support for basic research across the Institute's mission, to gain further insights into health and disease and propel new ideas for interventions. Examples include research to identify type 2 diabetes risk genes in minority populations disproportionately affected by this disease; to discover environmental factors that trigger type 1 diabetes in genetically susceptible individuals; to elucidate the causes and consequences of a form of diabetes that can strike people with cystic fibrosis; to increase understanding of intestinal stem cells, which could benefit a variety of digestive diseases; and to augment knowledge of blood cells and hematologic diseases.

PREVENTING AND TREATING DISEASE—IN CLINICS AND COMMUNITIES

Through innovative design and rigorous testing of interventions—whether in the operating room, doctor's office, or home or community settings—NIDDK-supported researchers are improving lives with new approaches to prevent, treat, and reverse diseases and disorders. For example, investigators previously showed that intensive blood glucose control, beginning soon after diagnosis of type 1 diabetes, reduced early signs of complications; now, after an average 22-year follow-up, the researchers demonstrated that controlling blood glucose reduced the risk of developing kidney disease by 50 percent, preserving kidney function for decades. The first cystic fibrosis therapy targeting a specific molecular defect gained U.S. Food and Drug Administration (FDA) approval. This important advance was a culmination of research supported in part by NIDDK, from the historic gene discovery (by the NIH Director) to clinical trials of the drug. With cutting-edge tissue engineering, researchers have successfully generated urethras to replace defective tissue and ameliorate urination difficulties in boys. A network of investigators found that vitamin E helps reduce fatty liver disease in children. In studies that may alert clinicians to patients with heightened need for intervention, scientists found that elevated levels of the hormone FGF–23 mark increased risk for heart disease and death in people with chronic kidney disease, while high levels of certain amino acids in the blood signify increased risk for type 2 diabetes.

Looking forward, NIDDK is committed to continuing funding for clinical research. Because many diseases within our mission disproportionately affect certain populations, we will also continue to seek insights and answers to health disparities. As just a few examples of our many clinical studies, Institute-supported scientists will conduct trials of approaches to prevent or slow the onset of type 1 diabetes, and they will press forward in developing technology to create an artificial pancreas for people with diabetes. In a new effort, the Institute is planning a comparative effectiveness study of commonly used drugs for type 2 diabetes. We will also continue a promising, long-term clinical trial of a lifestyle intervention designed to promote weight loss and improve health in obese people with type 2 diabetes. Among multifaceted efforts to meet the challenge of obesity will be a consortium studying lifestyle interventions for overweight and obese pregnant women, to improve the health of both mother and child. The Institute will continue to support clinical studies for a range of liver diseases; for example, a multicenter research network is planning trials of different treatment strategies for hepatitis B, including comparative effectiveness research. Multiple efforts will pursue approaches to combat chronic kidney disease, polycystic kidney disease, primary glomerular disease, and other forms of kidney disease and injury. We have also spearheaded an initiative encouraging studies to prevent and treat obesity, diabetes, and kidney disease in military populations. NIDDK continues to support a multi-disciplinary study in chronic urologic

pelvic pain, and will support a new research network to improve measurement of the complex symptoms of lower urinary tract dysfunction in men and women and to advance clinical studies. To maximize the reach and benefits of interventions proven successful in clinical trials, we will sustain support for translational research, to implement these in real-world medical practice and community settings, cost effectively, for diverse populations. For example, an NIDDK-funded research project provided the first demonstration that YMCAs, now officially called Ys, can deliver a group-based version of the lifestyle intervention shown to reduce type 2 diabetes in the Diabetes Prevention Program clinical trial.

SUPPORTING AN INNOVATIVE, MULTIDISCIPLINARY WORKFORCE

Research breakthroughs happen only through the efforts of a creative, well-trained workforce. Thus, NIDDK will continue programs to train and support researchers at all stages of their careers, and to ensure that we benefit from the best scientific minds. NIDDK supports summer research opportunities for underrepresented high school and college students, workshops for minority investigators and new investigators, a new initiative for professional societies to promote diversity in the research workforce, and other efforts. We will continue to support investigator-initiated projects, along with solicited research that is guided by input from expert researchers and the public.

INTEGRATING SCIENCE-BASED INFORMATION INTO PRACTICE

We will also continue to support education, outreach, and awareness programs. These efforts include materials tailored for diverse audiences and span the range of diseases within our mission, to bring vital, science-based knowledge to healthcare providers, patients and their families, and the general public.

In closing, NIDDK's future research investments will build upon findings from past and ongoing studies, pursue promising new opportunities, and tackle critical challenges toward innovative and more effective prevention and treatment strategies. Our research will be guided by five principles:

—maintain a vigorous investigator-initiated research portfolio;
—support pivotal clinical studies and trials;
—preserve a stable pool of new investigators;
—foster research training and mentoring; and
—disseminate science-based knowledge through education and outreach programs.

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Cancer Institute (NCI) of the National Institutes of Health (NIH). The fiscal year 2013 NCI budget of $5,068,864,000 includes an increase of $2,717,000 more than the comparable fiscal year 2012 level of $5,066,147,000.

As many of you will read upon its release later today, the 2012 annual report to the Nation on the status of cancer offers a generally encouraging view of cancer trends. The report documents that death rates from all cancers combined for men, women, and children in the United States continued to decline between 2004 and 2008, the latest year for which we have complete analysis. Age-adjusted mortality rates for 11 of the 18 most common cancers among men and for 14 of the 16 most common cancers in women have declined. The overall rate of new cancer diagnoses, also known as incidence, among both men and women also declined over similar periods, although for women the decline leveled off from 2006–2008.

These continued declines in death rates for most cancers, as well as the overall drop in incidence, are powerful evidence that our Nation's investment in many fields of cancer research produces life-saving approaches to cancer control. The breadth of the Nation's cancer portfolio and our ability to pursue many different approaches to cancer research must match the heterogeneity of cancer itself, which we now understand to be literally hundreds of genetically distinct diseases with many avenues to prevention, screening, diagnosis, and treatment.

BASIC AND SCIENCE

A large part of the NCI basic research portfolio uses molecular biology and genetics to deepen our knowledge about the origins and behavior of cancers and to develop drugs and understand drug resistance. For example, decades of basic research culminated in development of the molecularly targeted drug Gleevec (imatinib). Since the U.S. Food and Drug Administration (FDA) approved the drug in 2001, it

has been the treatment of choice—and a very effective one—for chronic myelogenous leukemia (CML) as well as a few other cancers. Targeted drugs usually inhibit enzymes—in this case, kinases—that are essential to the survival of cancer cells, rather than broadly killing all rapidly dividing cells in the body. In CML, the target is the abnormal protein made by fused genes, BCR–ABL, in cancerous blood cells, where in its activated or "on" state the mutant enzyme pushes white blood cells into overdrive, causing disease. Gleevec blocks the mutant enzyme, kills cancer cells, and returns the blood system and the patient to a normal state.

But despite Gleevec's generally powerful effects, some CML patients relapse when new mutations make the BCR–ABL protein resistant to Gleevec, allowing the abnormal enzyme to drive white blood cell growth again despite treatment. This phenomenon, drug resistance, is now being encountered with the several other targeted therapies more recently introduced for lung cancer, melanoma, and other cancers. So it is encouraging to report that NCI-supported research has identified a number of drugs targeting BCR–ABL proteins even after they acquire mutations that confer resistance to Gleevec. Two of these, approved a few years ago, did not overcome relatively common resistance mutation. But a third generation of drugs is able to do that, in an interesting new way, by freezing the target protein in an inactive conformation, so that its enzyme cannot work. This example illustrates another important point. Many different research streams—from genetics to structural biology to pharmacology—were required for these advances in treatment. The need to bring together multidisciplinary teams to focus on key questions like drug resistance in cancers increasingly defines modern biomedical research.

To strengthen NCI's ability to drive similar discoveries, NCI this year consolidated a number of its genomics initiatives—including the flagship program The Cancer Genome Atlas (TCGA)—into a single Center for Cancer Genomics. TCGA's aim is to characterize comprehensively the genomic alterations in hundreds of samples of about 20 known tumor types. With the project nearing completion on schedule, the vast influx of data promises to dramatically alter our knowledge of the genetic changes that drive cancer development. The new center will work with other components of NCI to ensure that the findings are applied to developing new diagnostics and therapeutics and are integrated swiftly into medical practice.

SCREENING AND PREVENTION

Early detection of cancer can enhance therapy. Last year I briefed this subcommittee on the recently concluded National Lung screening trial, which had demonstrated that current and former smokers who were screened with low-dose helical computed tomography were 20 percent less likely to die of lung cancer compared to others who received standard chest xrays.

Recent findings from another long-term study also point to screening as an effective way to cut deaths from another common cancer—colorectal adenocarcinoma, which kills about 49,000 Americans every year. Clinical studies, several funded by NCI, have consistently demonstrated that tests for fecal blood and direct observation of the colon with endoscopy can effectively reduce the mortality rates associated with colorectal cancer—by up to 50 percent, according to one recent estimate. NCI also is investing in studies to understand behavioral and economic barriers to screening to increase screening rates, especially among minority populations.

DIAGNOSIS AND TREATMENT

One of the most critical aspects of cancer is its remarkable heterogeneity—cancer is actually a collection of hundreds of genetically distinct diseases, each with its unique vulnerabilities. Lung adenocarcinomas, for instance, develop through a variety of genetic changes, and each pattern of changes requires a different therapeutic approach. Just a few years ago, it was recognized that up to 7 percent of lung adenocarcinomas contain a fused chromosome that activates the protein made by a gene called ALK to cause cancerous growth. FDA last fall approved crizotinib to treat patients with the abnormal ALK gene. Crizotinib blocks the activity of the enzyme, again a kinase, produced by the fused ALK gene, similar to the action of Gleevec in CML. This oral drug has been approved by the FDA and must be used with a companion molecular test to make sure it is used to treat only tumors with the abnormal ALK gene.

Another potential treatment recently emerged from academic research laboratories, this one for metastatic prostate cancer. MDV–3100 is a so-called anti-androgen therapy that prevents male hormones from stimulating the growth of prostate cancer cells through androgen receptors—preventing testosterone from binding to androgen receptors and preventing the androgen receptor from initiating the production of proteins that induce tumor growth. Current anti-androgen drugs

suppress the growth of prostate cancer cells temporarily, but in most patients, the cancer ultimately develops resistance to these drugs by increasing the amount of receptors. MDV–3100, by contrast, binds so tightly to the androgen receptors that it prevents them from functioning even when the receptor numbers are very high. The new drug performed so well that the clinical trials were halted early, and the drug now awaits approval at FDA.

PROVOCATIVE QUESTIONS

During the past 14 months, NCI has brought together researchers to propose, craft, and debate what they consider to be the critical questions in cancer research that may fall outside our current sphere of focus, but that could lead to important discoveries about the causes and behaviors of cancers. NCI convened 17 workshops across the country that identified some 24 provocative questions, and NCI has set aside an initial $15 million from its fiscal year 2012 budget to fund some of the more than 750 applications received under this program. While this initiative does not replace NCI's longtime and essential emphasis on funding investigator-initiated research, it represents a useful new approach to making the greatest impact with our research dollars.

The Congress's past investments in cancer research are the reason we are able to report promising scientific findings each year, and why the report to the Nation continues to show steady progress against a wide range of cancers. We are now able to define genetic changes that cause cancer, use them to control cancer with more precise tools, and thereby reduce the Nation's cancer burden. The President's budget for 2013 for the NCI will provide the support for discoveries in basic science, cancer control and prevention, for early detection and diagnosis, and for methods to prevent, treat, and in some instances, cure cancers.

PREPARED STATEMENT OF RICHARD J. HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING

Mr. Chairman and members of the subcommittee: I am pleased to present the President's fiscal year 2013 budget request for the National Institute on Aging (NIA) of the National Institutes of Health (NIH). The fiscal year 2013 budget includes $1,102,650,000, which is $522,000 more than the comparable fiscal year 2012 level of $1,102,128,000.

More than 40 million people age 65 and older live in the United States, and data from the Federal Interagency Forum on Aging-Related Statistics indicate that their numbers will double by 2040. In less than 50 years, the number of "oldest old"—people ages 85 and older—may quadruple. As record numbers of Americans reach retirement age and beyond, profound changes will occur in our economic, healthcare, and social systems.

NIA leads the national effort to understand aging and to identify and develop interventions that will help older adults enjoy robust health and independence, remain physically active, and continue to make positive contributions to their families and communities. We support genetic, biological, clinical, behavioral, and social research related to the aging process, healthy aging, and diseases and conditions that often increase with age. We also carry out the crucial task of training the next generation of researchers who specialize in understanding and addressing the issues of aging and old age.

BUILDING MOMENTUM IN THE FIGHT AGAINST ALZHEIMER'S DISEASE

Estimates of how many people in the United States currently have Alzheimer's disease (AD) range from 2.7 to 5.1 million, depending on how AD dementia is defined and measured. However, scientists agree that unless the disease can be effectively treated or prevented, the numbers will increase significantly if current population trends continue.

At the same time, there has never been greater cause for optimism. In recent years, we have expanded our understanding of how the disease takes hold and progresses, identified promising targets for intervention, and developed new models to speed discovery. For example, researchers have developed a mouse model that expresses human tau, one of AD's pathological hallmarks, and discovered that tau pathology is transmitted from cell to cell, beginning in the brain's entorhinal cortex and spreading from one brain region to the next. This discovery provides insight into AD's earliest development and offers a model for testing mechanisms and functional outcomes associated with disease progression. In another study, investigators "reprogrammed" human skin cells into induced pluripotent stem cells, which then

differentiated into working neurons; this breakthrough will facilitate the study of AD in human neurons and provide important insight into the etiology of the disease.

Advances in imaging technology, most notably through the NIH-supported Alzheimer's Disease Neuroimaging Initiative (ADNI), have expanded our ability to understand the underlying pathology of AD, diagnose the disease, track the progress of interventions, and even identify individuals at risk. ADNI data were also used last year to develop new, more comprehensive diagnostic guidelines at both the clinical and pathological levels.

NIH currently supports more than 35 clinical trials, including both pilot and large-scale trials, of a wide range of interventions to prevent, slow, or treat AD and/or cognitive decline; more than 40 compounds are in preclinical development through the AD Translational Initiative. NIA also participates in the NIH Neuroscience Blueprint under which investigators developing new compounds will have access to drug development services not typically available to the academic research community.

Investigators are also "re-purposing" treatments for other diseases as treatments for AD, with encouraging results. For example, a pilot clinical trial recently demonstrated that a nasal-spray form of insulin was able to delay memory loss and preserve cognition in people with cognitive deficits ranging from mild cognitive impairment (often a precursor condition to AD) to moderate AD. In a separate study, the skin cancer drug bexarotene promoted clearance of amyloid-beta and reversed cognitive deficits in mice. These preliminary findings offer new and exciting possibilities for the effective prevention and treatment of AD.

NIA has been an active participant in the implementation of the National Alzheimer's Project Act, including the development of a national plan to address AD. A new Presidential initiative to boost support for AD research, which will provide an additional $50 million in fiscal year 2012 and $80 million in fiscal year 2013 for the disease, will stimulate and support important groundbreaking work in a number of areas, including AD-extensive whole genome sequencing to identify genetic risk and protective factors for AD. Our activities will be informed by input from expert advisors participating in the May 2012 Alzheimer's Disease Research Summit.

UNDERSTANDING AGING AT THE MOST BASIC LEVEL

NIA initiatives on the molecular mechanisms of aging, from in-depth study of single cells to the broad study of organisms at the systems level, continue to advance our understanding of the basic underpinnings of the aging process. For example, investigators recently found that it was possible to delay onset of age-related changes in the skeletal muscle, fat, and eye tissues in mice by removing senescent cells—i.e., cells that are alive but no longer functional. The study also found a slowing of progression of age-related disorders in the mice. These results suggest that cell senescence may be a fundamental mechanism that drives aging.

IMPROVING THE HEALTH AND WELL-BEING OF OLDER AMERICANS

As the American population continues to age, it is imperative that we identify the optimal means to address the unique health needs of older individuals. For example, the Centers for Disease Control and Prevention reports that fully one-half of older Americans have at least two chronic health conditions that compromise quality of life. NIA is participating in a trans-NIH initiative to develop interventions to modify behavior and improve health outcomes among individuals with or more chronic conditions.

Increased adherence to recommended medication regimens promises substantial improvements in public health as well as savings in healthcare costs. NIA-supported investigators found that simply encouraging people to write down the time and date when they plan to receive a flu vaccination can significantly increase vaccination rates. NIA also participates in an NIH-wide initiative to identify practical interventions to improve medication adherence in the primary care setting.

Studies have shown that regular physical activity can improve physical performance in older people, but definitive evidence that physical activity can prevent mobility disability is lacking. NIA supports the Lifestyle Interventions and Independence for Elders Study to assess the effects of a structured physical activity program in 1,600 sedentary older individuals. With the U.S. Surgeon General, NIA has also launched its nationwide Go4Life campaign to motivate older Americans to engage in physical activity and exercise.

In the past year, preliminary results were released from the "Oregon Lottery" study, in which randomly selected low-income Oregon residents were able to enroll in the State's Medicaid program. Compared to a control group, the new Medicaid enrollees reported improved health and well-being, as well as reduced financial

strain. Use of important types of healthcare services such as preventive care also increased.

EMPOWERING THE NEXT GENERATION OF AGING RESEARCHERS

The need for healthcare professionals who specialize in the unique needs of older individuals is becoming ever more urgent. We must not only increase the number of practicing physicians trained in geriatrics and in subspecialty fields related to the health problems of elders but also foster the development of the next generation of physician-scientists whose clinical research will lead to improved care and more effective treatment options for older patients with complex medical conditions. Recently, NIA established the Grants for Early Medical/Surgical Subspecialists' Transition to Aging Research (GEMSSTAR) program to promote future leaders in clinical aging research through support of physicians who seek to become clinician-scientists in geriatric aspects of their subspecialty. NIA has also established a program targeting undergraduate students from diverse backgrounds in order to advance their interest in and knowledge of aging issues.

THOMAS R. INSEL, M.D., ACTING DIRECTOR, NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

Mr. Chairman and members of the subcommittee: It is a privilege to present to you the President's budget request for the newly established National Center for Advancing Translational Sciences (NCATS) for fiscal year 2013. The fiscal year 2013 budget of $639,033,000 includes $64,320,000 more than the comparable fiscal year 2012 level of $574,713,000. We are thankful for your support for this new Center and look forward to sharing progress with you as the Center evolves.

Our mission is to catalyze the generation of innovative methods and technologies that enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. As such, NCATS will focus on addressing scientific and technical challenges in order to reduce, remove, or bypass significant hurdles across the continuum of translational research. These advances will enable others in both the public and private sectors to develop drugs and diagnostics more efficiently for any number of human diseases—ultimately accelerating the pace in which new therapeutics are delivered to the patients who need them.

FULFILLING OUR MISSION

In achieving its aims, NCATS activities will be guided by three important principles:

—facilitate—not duplicate—other translational research activities supported by NIH;

—complement—not compete with—efforts already underway in the private sector; and

—reinforce—not reduce—NIH's commitment to basic research.

These guiding principles underscore the role of NCATS as a catalytic hub for evidence-based research on the process of translating scientific discoveries into new diagnostics and therapeutics.

Key to the success of the NCATS mission is identifying, studying, and reducing significant bottlenecks in the process of translation, which will require extensive consultation with experts across disciplines and sectors. NIH held numerous workshops for stakeholders to solicit ideas for the NCATS research agenda. A working group of several NIH Institute and Center directors, including those most involved in translational research, clarified the need for a new effort focused on the discipline of translation, providing tools and resources that could facilitate research across NIH. A working group of the NIH advisory committee to the Director, comprised of experts from industry, private equity firms, nonprofits, and academia identified the need for NCATS to catalyze, invigorate and streamline translational sciences nationally and globally. Many areas of priority were identified, including research on biomarkers, predictive toxicity, target validation, regulatory science and de-risking the pipeline. The perspectives of both of these working groups are reflected in several of the NCATS initiatives being pursued, ensuring that NCATS is not duplicating other efforts at NIH or competing with efforts in industry.

NCATS is currently assembling an advisory structure comprising both the NCATS advisory council and the Cures Acceleration Network (CAN) review board. These individuals will span many sectors, from patient advocacy organizations to pharma-

ceutical industry and private equity firms, along with renowned experts in translational science and regulatory review.

CATALYZING INNOVATION IN CLINICAL RESEARCH

Re-engineering and accelerating the clinical research enterprise is a major priority for NCATS. The Clinical and Translational Science Awards (CTSAs), which represent nearly three quarters of the proposed NCATS budget, will lead our efforts to re-engineer and accelerate clinical research. Across the Nation, CTSA institutions have been supporting first-in human trials for rare and common diseases; developing and testing innovative trial designs; and developing postmarketing clinical research. Since the first awards in 2006, the CTSAs have transformed clinical research in academic medical centers, creating new homes for translational science, integrating communities into the research process, and training a new generation of interdisciplinary clinical researchers. An external evaluation of the CTSA program has been conducted and offers constructive recommendations for ensuring that this highly valuable program is optimally leveraged and aligned with NCATS as we move forward.

To accelerate research, the CTSAs have developed innovative informatics tools, such as REDcap, a freely available tool for clinical study management and capture, and ResearchMatch, a free, secure, Web-based registry which now has more than 20,000 volunteers for research studies and enables researchers to find the "right match" to participate in studies.

In 2013, we will be launching CTSA 2.0, the next phase of this program building on the successes of the past 6 years. While CTSA 1.0 established homes for translational research, CTSA 2.0 can create neighborhoods, networks of centers with shared resources to accelerate research on rare diseases and new therapeutics. Going forward, the CTSAs can have an even broader role on translational science, supporting the entire pipeline of development from bench to bedside, bedside to practice, and beyond practice to public health policy.

CATALYZING INNOVATION IN THERAPEUTICS

Drug development is expensive, slow, and failure prone. Approximately 90 percent of compounds that advance to clinical testing fail to reach the market. While NCATS will not create an industrial drug development pipeline, it can experiment on the process, identifying solutions for specific problems in drug development.

For instance, of the most common concerns we heard from industry, patient groups, and the Food and Drug Administration (FDA), was the need for detecting toxicity early in the drug development process. Roughly one-third of the failures of new medications can be attributed to toxicity not predicted from preclinical (animal or in vitro) studies. NCATS is working with the Defense Advanced Research Project Agency (DARPA) and the FDA to design a chip composed of diverse human cells and tissues with read outs that can detect toxicity. This "tissue chip" should make drug safety assessments more accurate and even make them possible earlier in the translational pipeline. DARPA and NIH have committed approximately $70 million each over 5 years and FDA will provide guidance. The first applications were received in late January 2012 and will be funded this year with partial support from the NIH common fund.

Aside from predicting toxicity, NCATS will be working on another innovation to speed medication development. Repositioning drugs that have not been approved (drug rescue) and drugs that are already approved (drug repurposing) are probably the most rapid and cost effective approaches to new therapies. As industry holds many of the assets and data required for efficient rescue and repurposing, many institutes at NIH have been interested in working with companies to access specific compounds. Rather than creating 26 different approaches, NCATS is working with industry to provide a single, comprehensive mechanism with several companies for drug rescuing. This will permit investigators and small businesses to apply for NIH funding to conduct research on new indications using compounds from industry-provided drug collections.

NCATS is also innovating the process of drug repurposing. Through the NCATS Pharmaceutical Collection, we have developed a comprehensive database of 3,800 approved and investigational drugs to permit NCATS to screen all existing medications for novel effects that might be therapeutic for a new indication. With this approach, we discovered that a drug approved for rheumatoid arthritis could be a novel treatment for leukemia. Rather than requiring 6–8 years for the usual preclinical research and development, we moved this approved compound into a leukemia trial (in a CTSA institution) within 9 months. Continued funding of this program in fiscal year 2013 will contribute to the NIH effort of decreasing the time,

cost, and attrition rate in therapeutic development, to bring more promising new therapies to the public.

SUPPORT FOR RARE AND NEGLECTED DISEASES

There are more than 6,000 rare diseases, affecting an estimated 25 million Americans. Fewer than 250 of these rare diseases have treatments, according to data from the Online Inheritance in Man Database, Orphanet, and FDA. It is clear that efforts need to be directed to increasing the number of treatments either through new or repurposed drugs. The Therapeutics for Rare and Neglected Diseases (TRND) program within NCATS develops treatments for rare diseases, with 20 projects currently underway. But TRND is not a typical drug development effort—the projects are selected as experiments on the pipeline of drug development. That is, each project is an attempt to re-engineer the process in addition to addressing a medical need. For instance, a project on sickle cell disease has introduced a new class of molecules not previously considered as medications for any disease. Moreover, the study of rare diseases, including many single gene disorders (Niemann-Pick Type C and Hereditary Inclusion Body Myopathy), is also giving us new insights into fundamental biology. This process, sometimes called reverse translation because it moves from "bedside to bench," is one of the ways that NCATS is reinforcing rather than reducing NIH's commitment to basic research.

INVESTING IN PEOPLE

NCATS fosters the training of clinicians and researchers in an environment of innovation and collaboration, encouraging the next generation of leaders in translational sciences. For example, the CTSAs are currently supporting more than 900 trainees across a wide array of disciplines. NCATS will promote novel training mechanisms, such as drug development apprenticeships for early-stage investigators, and explore cross-training of physicians and scientists between industry and academia.

CONCLUSION

The creation of NCATS offers an exciting new opportunity for accelerating the development of new and more effective therapeutics and diagnostics; namely by approaching the process of translation as a scientific challenge. By encouraging biomedical researchers across the Nation to experiment with new and innovative ways of improving these processes, our best and brightest can meet today's challenges head on. Moreover, the development of new tools and methodologies enable all sectors to participate in this arena, maximizing the likelihood of ensuring much needed products are actually available to those who need it the most—patients.

PREPARED STATEMENT OF JAMES F. BATTEY, JR., M.D., PH.D., DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Institute on Deafness and Other Communication Disorders (NIDCD) of the National Institutes of Health (NIH). The fiscal year 2013 NIDCD budget of $417,297,000 includes an increase of $1,519,000 over the comparable fiscal year 2012 level of $415,778,000.

The NIDCD conducts and supports research and research training in the normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language. Our Institute focuses on disorders that affect the quality of life of millions of Americans in their homes, workplaces, and communities. The physical, emotional, and economic impact for individuals living with these disorders is tremendous. NIDCD continues to make investments to improve our understanding of the underlying causes of communication disorders, as well as their treatment and prevention. It is a time of extraordinary promise, and I am excited to be able to share with you some of NIDCD's ongoing research and planned activities addressing communication disorders.

EARLY EXPERIENCE SHAPES SALT PREFERENCE

Even though we know that too much salt is bad for our health, many of us still consume too much of it. In a typical diet, a lot of salt comes from starchy foods, such as breads and cereals. Too much salt can cause high blood pressure, or hypertension. Although hypertension itself usually has no symptoms, it can cause serious health problems such as stroke, heart failure, heart attack, and kidney failure. NIDCD-supported scientists determined that babies whose diets contain starchy,

salty foods will develop a preference for salty taste by as early as 6 months of age, as compared to babies who have not been given salty foods. During a preference test, the babies accustomed to saltier diets consumed 55 percent more salt than their unexposed peers. Salt preference endures into the preschool years, when children exposed to a salty diet as babies are more likely to consume plain salt. This research identifies a potential role for early dietary experiences in shaping taste preferences that could influence salt consumption in our adult years. If these results can be repeated in a larger study population, it suggests that we may be able to reduce salt consumption in future generations by encouraging parents to restrict salt in their babies' early diets. Reducing salt consumption will also reduce the incidence of hypertension, thus reducing healthcare costs due to hypertension and the serious health problems it can cause.

IDENTIFICATION OF MAJOR PROTEINS INVOLVED IN HEARING

According to NIDCD statistics, 2 to 3 out of 1,000 children in the United States are born deaf or hard of hearing, with changes in genes being a major cause of hearing impairment. NIDCD-supported scientists have shown that mutations in the TMC1 and TMC2 genes cause hereditary deafness in humans and mice. Further, they discovered that the proteins encoded by TMC1 and TMC2 genes may be key components of the long-sought after mechanotransduction channel in the inner ear—the place where mechanical stimulation of sound waves is transformed into electrical signals recognized by the brain as sound. Using mice without the TMC1 and TMC2 genes, the scientists discovered the mice had a deficit in the mechanotransduction channels in their sterocilia, the sound-sensing organelles of the inner ear, while the rest of the auditory hair cell's structure and function was normal. These genes and the proteins they regulate are the strongest candidates yet in the search for the transduction channel. If these genes do indeed encode the transduction channel, they will be useful tools to screen for drugs or molecules that bind to or pass through the channel and could be used to prevent damage to hair cells.

KEEP NOISE DOWN ON THE FARM

Farming is loud work. Squealing pigs, grinding combines, whirring power tools, and roaring vehicles can add up to a lot of noise. Prevention and treatment of noise-induced hearing loss (NIHL) is a priority for the NIDCD. NIDCD's campaign "It's a Noisy Planet. Protect their Hearing" promotes early education of elementary and middle-school children about NIHL and how to prevent it. The NIDCD has introduced new materials for parents of children who live and work on a farm to help them develop healthy hearing habits and protect their hearing for life. The NIDCD hopes that these materials will help protect individuals who live and work on a farm from developing NIHL. Preventing NIHL will improve quality of life for the millions exposed to noise, and decrease overall healthcare costs.

SALIVA IS EFFECTIVE IN SCREENING FOR CYTOMEGALOVIRUS INFECTION IN NEWBORNS

In June, NIDCD-supported scientists reported that swabbing a newborn's mouth for saliva can be used to quickly and effectively screen for cytomegalovirus (CMV) infection, a leading cause of progressive hearing loss in children. Scientists at the University of Alabama at Birmingham (UAB) determined that saliva correctly identified every baby born with the infection when liquid samples were used, and 97.4 percent of babies when the samples were dried. Most babies infected with CMV don't show symptoms at birth. NIDCD has placed a high priority on developing diagnostic tools to screen babies for congenital CMV infection, so that those who test positive can be monitored for possible hearing loss. These children can be provided with appropriate intervention as soon as possible. Because of this research, we know that testing saliva is an effective way to identify children at risk for hearing loss due to CMV.

HIV-EXPOSED CHILDREN AT HIGH RISK OF LANGUAGE DELAY

Children who do not use language well may not do well in school and may also have difficulty communicating with their peers and establishing friendships. A recent study funded by the NIDCD and seven other NIH Institutes found that 35 percent of a group of school-age children born to women with an HIV infection during pregnancy have difficulty understanding spoken words and expressing themselves verbally. These data should encourage those caring for children exposed to HIV in the womb to provide early treatment for language impairments.

PREPARED STATEMENT OF LINDA S. BIRNBAUM, PH.D., D.A.B.T., A.T.S., DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH). The fiscal year 2013 NIEHS budget of $684,030,000 includes a decrease of $725,000 less than the comparable fiscal year 2012 level of $684,755,000.

INTRODUCTION

As the Dutch philosopher Desiderius Erasmus so succinctly put it: Prevention is better than cure. In most instances, disease is a result of a combination of age, genetics, and environment. But unlike age and genetics, environment is something that we can affect in order to prevent illness. As an environmental public health institute, the NIEHS is entrusted with the mission to prevent human suffering and illness by creating and sharing the knowledge necessary for understanding the role of the environment in disease, and thereby enable people to lead healthier lives. NIEHS continually strives to lead public health prevention efforts by providing research science and translation to inform decisions and policies at the individual, community, national, and global levels that prevent hazardous environmental exposures and thus reduce disease and disability. Many of the most challenging diseases—and most costly in terms of both human suffering and economic resources—are being shown to have strong environmental components. Diseases such as cardiovascular disease and stroke, that cause 1 in 3 deaths in America each year, have been associated with exposure to environmental agents such as air pollution and secondhand smoke. An estimated nearly 70 percent of Americans older than the age of 20 are overweight or obese; for children the figure is more than 30 percent. New research, including studies funded by the NIEHS, shows that obesity and its common companion diabetes are complex disorders that are affected not just by food consumption and physical exertion but also by environmental factors including exposures to environmental contaminants during early life. Greater understanding of the role of such exposures and concomitant efforts to prevent them could dramatically change the trend of this increasing public health epidemic. And the list goes on. Strong associations have been shown between exposure of pregnant mothers to chemicals, including polybrominated diphenyl ethers added to products as flame retardants, and a range of neurodevelopmental disorders, learning disabilities, and behavioral effects in their children. NIEHS continues to commit significant efforts to increasing our understanding of these health effects and how they might be prevented. On a global level, the problem of respiratory illnesses resulting from exposure to indoor air pollution represents an area ripe for intervention. Toxic smoke from burning biofuels in cookstoves kills nearly 2 million people each year, largely women and children, according to the World Health Organization. NIEHS is part of the Global Alliance for Clean Cookstoves, a public-private initiative working to eliminate exposure to harmful cookstove smoke. This is a tractable prevention problem with a potentially huge payoff in public health.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES STRATEGIC PLANNING

Looking at this long list of environmentally related diseases raises the question, "How can one Institute have an impact on research and disease prevention in all these areas?" To answer this question, NIEHS is striving to maximize its impact and leadership in the environmental health sciences through a comprehensive and inclusive strategic planning process focused on identifying key strategic goals for the next 5 years. Through this process, NIEHS hopes to achieve its vision of providing a catalyst for leading the field of environmental health sciences in applying state-of-the-art biomedical research to the most important issues surrounding environmental impacts on health.

Six broad-based themes of this plan have been established, through ongoing dialogue with research scientists and stakeholder groups. "Fundamental Research" investigates basic biological pathways of how our bodies function, to set the stage for asking more in-depth questions about the effects of the environment on biological systems. "Exposure Research" focuses on the study of environmental exposures themselves, internal and external to the body. And since NIEHS recognizes that information is only effective if it can be translated into sound decisions, "Translational Science" is identified as a key theme covering research that moves a basic science observation into a public health or medical application. NIEHS also affirms its commitment to "Health Disparities and Global Environmental Health" in recognition of the fact that individuals and communities that are socioeconomically disadvantaged

also tend to suffer inequalities in both health and environmental burdens. Through "Training and Education," NIEHS recognizes the need to develop the next generation of top-notch, innovative, and dedicated environmental health scientists and professionals. Finally, to fulfill its mission and statutory mandate to disseminate information, NIEHS is committed to developing a full range of research translation and communication tools and creative stakeholder partnerships. This "Communications and Engagement" theme is vital for realizing the Institute's mission to promote public health and prevent environmentally related disease and disability. Two crosscutting themes, "Collaborative and Integrative Approaches" and "Knowledge Management" will be implemented across the other themes to ensure the success of the goals throughout the strategic plan.

RECENT ACCOMPLISHMENTS

The NIEHS strategic plan highlights areas of leadership that will build on an impressive list of recent research accomplishments. For example, NIEHS-funded researchers recently published the first study documenting how exposure to perfluorinated compounds (PFCs), widely used in manufactured products such as nonstick cookware, was associated with lowered immune response to vaccinations in children. Other recent research funded by NIEHS has shown that even moderate air pollution, at levels generally considered safe under current Federal regulations, increases the risk of stroke by 34 percent.

NIEHS is also committed to helping those impacted by environmental exposures. In the aftermath of the Deepwater Horizon disaster, many questions remain about the long-term impact on the health of gulf coast residents and communities. NIEHS is leading a trans-NIH effort to create a network of community and university partnerships that seeks to identify personal and community health effects stemming from the Deepwater Horizon oil spill and to enhance community resiliency to potential disasters. The 5-year, $25.2 million program will support population-based and laboratory research, which will ultimately develop the scientific evidence base needed to promote health and well-being for people living along the gulf coast who are at greatest risk for potential adverse physical, psychological, and behavioral health effects. In addition, research will seek to develop new strategies to enhance capacity to respond to future disasters and prevent or minimize adverse health effects arising from them. Once completed, research findings from the Deepwater Horizon Research Consortia should contribute to the evidence base needed to improve preparedness and response aimed at minimizing disaster-related health impacts.

Ultimately, NIEHS remains committed to its overall mission to discover how the environment affects people's health, in order to promote healthier lives.

PREPARED STATEMENT OF JOSEPHINE P. BRIGGS, M.D., DIRECTOR, NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Mr. Chairman and members of the subcommittee: As the Director of the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH), I am pleased to present the President's fiscal year 2013 budget request for NCCAM. The fiscal year 2013 budget includes $127,930,000, which is $26,000 more than the comparable fiscal year 2012 level of $127,904,000.

The landscape of our healthcare system is changing in many important ways. Among them is a clear trend toward incorporation of complementary health practices, which often have origins outside of conventional medicine, into integrative approaches to care. There are a number of factors—including consumer demand and emerging scientific evidence—driving these changes. Nonetheless, there are compelling needs of the public, healthcare providers, and policymakers for good scientific evidence on the safety and potential benefit of these complementary and integrative approaches. Using the highest standards of scientific rigor, NCCAM is committed to developing evidence about practices that are being integrated into healthcare. We are particularly interested in those cases where there is scientific opportunity and/or important public health need.

TRENDS IN COMPLEMENTARY AND INTEGRATIVE HEALTHCARE

National surveys conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention show that nearly 40 percent of Americans report using one or more practices such as acupuncture, massage, yoga, meditation, spinal manipulation, dietary supplements, or herbal medicines to help manage their health and wellness. Similarly, data show that healthcare systems and providers are incorporating such interventions. For example, an American Hos-

pital Association survey conducted in 2007 showed that 37 percent of hospitals offered complementary modalities; and a national study reported last year by the NCHS reported widespread availability of complementary approaches in hospice settings. Other data from the Departments of Defense (DOD) and Veterans Affairs (VA) show increasing use of complementary modalities in their populations. According to the VA, 89 percent of their facilities offered complementary therapies in 2011. Both the DOD and VA have integrated complementary modalities into the care of patients with post-traumatic stress and sleep disorders, and to improve treatment of pain.

REDUCING PAIN AND IMPROVING SYMPTOM MANAGEMENT

One area of urgent public health need is better strategies for managing chronic pain. According to the Institute of Medicine, chronic pain affects an estimated 116 million Americans, and costs the Nation approximately $635 billion each year. Chronic pain is the most frequently cited reason for which Americans use complementary health practices. For many individuals suffering from chronic pain, conventional approaches provide incomplete relief. Furthermore, pharmacological treatment with opioids or anti-inflammatory drugs can have significant adverse effects. There is now emerging evidence, much of it from NCCAM-supported studies, that some nonpharmacological interventions, such as massage, spinal manipulation, yoga, meditation, and acupuncture, may be helpful in treating chronic pain. Additional scientific evidence is needed to better understand these findings, and the optimal use and safety of these integrative approaches.

To this end, NCCAM is supporting a growing portfolio of studies on the use of nonpharmacological interventions for the management of chronic pain, including back and neck pain and pain associated with osteoarthritis, fibromyalgia, and headaches. In addition, we are supporting research to better understand the biological mechanisms by which complementary modalities may contribute to management of pain and other symptoms. For example, we recently funded Centers of Excellence for Research on Complementary and Alternative Medicine that use advanced functional and structural neuroimaging technologies to study pain. NCCAM is also providing leadership to a working group within the trans-NIH Pain Consortium to develop standards for research on chronic low back pain. Finally, in the next year, NCCAM plans to focus its intramural research program on understanding the role of the brain in chronic pain syndromes. The program will be highly collaborative with other intramural neuroscience programs on the NIH campus.

ADVANCING RESEARCH ON NATURAL PRODUCTS

NCCAM remains strongly committed to developing better evidence and information resources on the safety and efficacy of commonly used natural products. The Center is targeting investment in research in this arena on understanding the biological mechanisms of these products, thus creating the translational foundation for subsequent human studies.

In addition, research examining issues of safety is of great public health importance, given the widespread availability and use of these products by the public. In this regard, one area of specific need is rigorous scientific information about interactions of these products with drugs or with other natural products. This spring, NCCAM will lead a workshop, cosponsored by the NIH Office of Dietary Supplements and the National Cancer Institute, with researchers from a variety of fields to discuss ways to improve the methodologies needed to study herb-drug interactions. Workshop recommendations will help guide NCCAM's research agenda.

BUILDING AND DISSEMINATING RIGOROUS EVIDENCE

Researchers studying the effectiveness and safety of healthcare approaches already in widespread use face methodological challenges, challenges that are not unique to NCCAM's mission. To develop better methods of studying health outcomes in real-world settings, NCCAM is leading an NIH Common Fund Initiative, the Health Care Systems Research Collaboratory. The Collaboratory will develop innovative research partnerships with healthcare delivery organizations to maximize the potential use of electronic health information. NCCAM is also exploring possible collaborations with the DOD and the VA, aiming to leverage the data being gathered on the use of complementary and integrative practices in their healthcare systems. Additionally, NCCAM is providing leadership and support to the trans-NIH Patient-Reported Outcomes Measurement Information System (PROMIS), which will provide clinicians and researchers with more efficient and reliable means for gathering data on a variety of patient-reported measures of health and well-being.

NCCAM continues to provide reliable, objective, and evidence-based information on the usefulness and safety of complementary health practices to the public and healthcare providers. For example, NCCAM publishes the Clinical Digest (nccam.nih.gov/health/providers/digest), a monthly e-newsletter that summarizes the state of the science on complementary health practices and clinical guidelines. Additionally, NCCAM provides an online resource (nccam.nih.gov/health/providers) that enables healthcare providers to make informed recommendations.

CONCLUSION

Strong consumer use of complementary health practices, and growing integration of these practices into a variety of conventional healthcare settings are important trends in U.S. healthcare. While there is emerging evidence of promise for some, there are many important unanswered questions about effectiveness and safety. NCCAM remains committed to building the scientific evidence needed by consumers, providers, and health policy makers to make informed decisions about the use of complementary and integrative health practices.

PREPARED STATEMENT OF ROGER I. GLASS, M.D., PH.D., DIRECTOR, FOGARTY INTERNATIONAL CENTER

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the Fogarty International Center (FIC) of the National Institutes of Health (NIH). The fiscal year 2013 FIC budget of $69,758,000 includes an increase of $219,000 more than the comparable fiscal year 2012 level of $69,539,000.

These are exciting times for global health. New HIV prevention strategies and the use of mobile technologies to extend the reach of health interventions are just two examples of research into emerging opportunities that can transform our efforts to improve health around the world. These are also examples of advances that can make a significant impact on health here at home as well as abroad. As populations in both the developed and developing world are vulnerable to existing and emerging infectious agents, as well as the growing noncommunicable disease (NCD) epidemic, there is no longer a "them" in global health, only an "us" (Global Health Council).

To most effectively address this shared burden of disease, U.S. scientists can only benefit from the unique insights and collaboration of skilled research partners around the world. At the NIH and within the U.S. Government, FIC plays a unique role by supporting the development of global health research expertise in the United States and abroad, and by fostering the international partnerships that extend the frontiers of science, accelerate discovery, and enable the United States to continue to lead in addressing the world's most pressing health challenges.

STRENGTHENING SUSTAINABLE RESEARCH CAPACITY

For over two decades, Fogarty has supported the long-term training of thousands of scientists worldwide. These scientists provide unique insights and perspectives on how to best combat global health challenges, and often contribute to groundbreaking research advances in collaboration with U.S. partners.

As the largest international commitment by any one country to fight a specific disease, the President's Emergency Plan for AIDS Relief (PEPFAR) relies on trained scientists to provide an evidence base for the new and effective strategies that have enabled PEPFAR programs and policies to make significant contributions to the progress toward an AIDS-free generation. For example, with support from Fogarty's longstanding HIV/AIDS research training program, Fogarty-supported researchers have provided evidence that a new, simpler, and shorter treatment regimen of antibiotics can prevent those infected with the tuberculosis (TB) bacterium—particularly those who also have HIV—from developing full-blown TB. In addition, Fogarty-supported researchers and trainees have also helped demonstrate: the effectiveness of anti-retroviral therapies in stopping mother-to-child transmission of the HIV virus; that male circumcision reduces HIV transmission to HIV-negative female partners; and a reduction in HIV transmission among women using microbicides that incorporate anti-retrovirals.

In response to the increased global burden of NCDs, Fogarty's NCD-Lifespan research training program supports partnerships between U.S. and low- and middle-income country (LMIC) institutions to build NCDs research capacity. By focusing on early childhood exposures and the genetic, environmental, and lifestyle risk factors that can contribute to later onset of disease, NCD-Lifespan projects are creating a cadre of investigators and institutions able to conduct research relevant to local and

global epidemics in areas such as cancer, stroke, mental illness, and metabolic disorders. In Ghana, for example, Fogarty is supporting the development of a Cardiovascular Research Training Institute as a partnership between New York University and the University of Ghana, to train investigators to conduct research on preventing and treating hypertension, diabetes, stroke, and chronic kidney disease. The resulting cadre of investigators will contribute research and expertise to the global effort to reduce cardiovascular disease morbidity and mortality.

With respect to identification of innovative, sustainable, and cost-effective strategies to fulfill its mission, Fogarty recognizes that information and communication technologies, mobile technologies, and distance learning can transform the way in which health and health research training can be conducted in the 21st century—particularly in resource-poor and remote settings. More than 50 Fogarty-supported projects have incorporated distance learning activities, which provide an innovative and cost-effective way to connect health research students in the developing world with state-of the-art content on the other side of the globe.

NEW INVESTIGATORS, NEW IDEAS

Over the last decade, American university campuses have seen a soaring interest in global health among students and faculty from diverse fields, placing U.S. universities in an excellent position to help generate solutions to complex global health challenges. Fogarty's International Clinical Research Scholars and Fellows program and International Research Scientist Development Awards capitalize on this groundswell of interest to invest in future American leaders in global health research. These programs are investing in the next generation of talented American scientists, who will develop the skills and sensitivities to conduct research in international settings, and engage talented local researchers who can help to address complex health challenges that affect populations in the United States and abroad. Former Scholars and Fellows have developed innovative solutions to concrete global health problems. For example, in Zambia, Dr. Krista Pfaendler developed and implemented an effective and low-cost cervical cancer screening program using digital cameras for cervical photography and acetic acid (vinegar) for visual inspection.

In 2010, Fogarty piloted a 1-year program to support postdoctoral investigators in U.S. universities to carry out innovative, multidisciplinary team research in global health. With support from this program, scientists developed point-of-care telemedicine units built with $2 microscopes that can be attached to a cell phone, enabling diagnosis of infectious diseases, such as malaria and HIV, in remote settings. Because of their ease of use, effectiveness, cost-effectiveness, and the ability for quick diagnosis, these microscopes have the potential to revolutionize care in resource-poor settings. The next generation of this program, Framework Innovations, will support U.S. and developing country institutions as they develop interdisciplinary postdoctoral research training programs in global health and enable young investigators to develop and test concrete and innovative health products, processes, and policies that respond practically and cost-effectively to critical health needs.

ADVANCING TRANSLATIONAL SCIENCE

Innovative strategies are needed to translate biomedical discoveries into new therapies, diagnostics, and prevention tools. Supported by Fogarty's International Cooperative Biodiversity Groups Program, United States and international scientists conduct discovery research on potential health applications of molecules—from plants, animals, and micro-organisms—and initiate partnerships with companies interested in developing these molecules for potential new drugs or diagnostics. This public-private partnership model has led to four active patents in the areas of cancer, parasitic diseases, and malaria.

CONCLUSION

As the world continues to become more interdependent, international scientific partnerships will play a critical role in building bridges between countries and scientists in the interest of advancing the health of our country and our globe. Fogarty invests in the best and brightest minds and catalyzes long-term, productive research collaborations. Working in partnership with the rest of the NIH, Fogarty's unique programs will continue to push the frontiers of science and enable scientists in the United States and abroad to work together to successfully tackle the world's most pressing and complex health challenges.

PREPARED STATEMENT OF PATRICIA A. GRADY, PH.D., RN, FAAN, DIRECTOR, NATIONAL INSTITUTE OF NURSING RESEARCH

Mr. Chairman and members of the subcommittee: I am pleased to present the President's fiscal year 2013 budget request for the National Institute of Nursing Research (NINR) of the National Institutes of Health (NIH). The fiscal year 2013 NINR budget of $144,153,000, includes a decrease of $444,000 less than the comparable fiscal year 2012 level of $144,597,000.

INTRODUCTION

I appreciate the opportunity to share with you a brief summary of some of the recent activities and future scientific directions of NINR. NINR supports clinical and basic research to build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms caused by illness, enhance palliative and end-of-life care, and train the next generation of scientists. In doing so, NINR promotes and improves the health of individuals, families, and communities across the lifespan, in a variety of clinical settings and within diverse populations. NINR's emphasis on clinical research and training places NINR in a position to make major contributions to developing the evidence base for science-driven practice through innovative treatment and behavioral research.

Over the past year, we have commemorated NINR's 25th anniversary at NIH through a series of scientific outreach events that culminated in October 2011 with the release of NINR's new Strategic Plan: Bringing Science to Life. As NINR looks ahead to the next 25 years, the Institute is well-positioned to continue to advance rigorous science, develop and support evidence-based science-driven interventions across the lifespan, develop future leaders in nursing science, and contribute to improving the Nation's health and national healthcare system.

ADVANCING THE QUALITY OF LIFE: SYMPTOM MANAGEMENT

With the aging of a major sector of the Nation and advances in treatment of formerly fatal diseases, we are faced with a population that is living with multiple chronic conditions. The challenge of treating and managing these multiple conditions and their associated symptoms is one that confronts nearly all health practitioners, especially nurses involved with chronic illness management. NINR has invested deeply in the area of symptom management, from funding basic research on pain in our Intramural Research Program (IRP) to our extramural support for psychosocial and nutritional interventions to improve symptoms of chronic heart failure. Further, recognizing that chronic illness strikes across the lifespan, NINR also supports research aimed at helping children and adolescents manage their own chronic conditions and their symptoms more effectively to improve their quality of life. Finally, NINR initiated a call for research on the interconnections of diabetes and asthma, both on the rise in the United States; this research is focused on early life exposures that are associated with both conditions, as well as interventions that target the management of each disease and their synergisms.

HEALTH PROMOTION AND DISEASE PREVENTION

NINR is also heavily committed to health promotion and disease prevention. Nurses are often in unique positions as the health providers with the most frequent interactions with individuals and their support networks, and are therefore well-poised to help develop interventions that promote health and prevent disease. In one example, NINR currently supports an innovative community-based program in urban Pennsylvania that trains male Latino lay health advisors who provide their peers information on community support resources, including healthcare resources. NINR also is leading a funding opportunity focused on developing healthy habits in children and adolescents that lead to lifelong sustainable healthy behaviors that prevent disease and disability. Finally, in line with our focus on health promotion and disease prevention across the lifespan, NINR supported a research project that developed a successful program to guide mothers of very preterm infants in correctly feeding their vulnerable infants.

INVESTING IN NURSE SCIENTISTS

NINR is strongly committed to the development of future health scientists, with a specific focus on the training of nurse scientists. Along with extramural research grants and fellowships that support pre- and postdoctoral students and junior and senior researchers, NINR offers a number of intramural training opportunities to develop nurse scientists. This year, we are proud to once again offer the NINR Summer Genetics Institute, a month-long, intensive course in genetics for nurse sci-

entists at all career levels. The course is designed to increase research in genetics among graduate students and faculty in nursing, and expand the knowledge base among clinicians for genetics in clinical practice. NINR also sponsors the Methodologies Boot Camp, a 1-week intensive research training course at NIH that focuses on applying state-of-the-art methodologies to studies of symptom management, including pain, fatigue, and sleep.

END OF LIFE AND PALLIATIVE CARE

With advances in treatment for chronic diseases and the aging of our population, we as a society are facing new challenges in understanding the complexities of decisionmaking issues surrounding palliative and end-of-life care for those with advanced illness. As the lead NIH Institute for end-of-life research, NINR is committed to supporting research that leads to science-driven practices in palliative care that assists individuals, families, caregivers, and healthcare professionals in alleviating symptoms and planning for end-of-life decisions. In August 2011, NINR convened a 3-day National Summit on, "The Science of Compassion: Future Directions in End-of-Life and Palliative Care." The Summit, co-sponsored by partners across NIH, examined the state of research and clinical practice in end-of-life and palliative care and, with almost 1,000 registrants, provided an opportunity for scientists, healthcare professionals, and public advocates to come together to catalyze and shape the future research agenda for this critical scientific area. NINR also supports, along with the NIH Office of the Director, a palliative care research cooperative to develop an enhanced evidence base for palliative care by facilitating multisite research studies and clinical trials.

INVESTING IN INNOVATION

NINR supports innovations that advance patient care, help lower the cost of healthcare, and take advantage of the advances in real-time personalized information on patients that guide healthcare today. For example, NINR supported two critical phases of the development of a novel "lab-on-a-chip" device for rapidly detecting HIV. The technique has proved highly successful, and the research team has gone on to refine and clinically test this microfluid-based lab-on-a-chip—or mCHIP—in real-life settings, with studies demonstrating that the mCHIP can accurately, rapidly, and cost-effectively detect clinically relevant infectious diseases in resource-limited settings. Other NINR-supported researchers have developed a novel, automated medication dispenser that reminds patients when to take medication, monitors dosage, and reduces treatment errors. The new dispenser will be the first on the market that can deliver not only all common forms of drugs but also biologically derived injectables.

CONCLUSION

Nursing science has a central role in developing the evidence-base for science-driven practices in healthcare. NINR's research agenda has guided and will continue to guide the advances in this field of health research through the implementation of our new Strategic Plan. NINR looks forward to continuing its support of innovative nursing science focused on some of the most important health and healthcare related issues of today.

PREPARED STATEMENT OF ERIC D. GREEN, M.D., PH.D., DIRECTOR, NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH). The fiscal year 2013 NHGRI budget of $511,370,000 includes a decrease of $893,000 less than the comparable fiscal year 2012 level of $512,263,000.

It is an extraordinary time for the field of genomics. Through recent scientific advances and technological developments, we are gaining a deeper understanding for how the human genome plays a central role in health and disease, enabling investigators across the biomedical research spectrum to pursue new avenues for translating this knowledge into clinical applications. NHGRI, guided by an ambitious vision for genomics research that the Institute published in February 2011, is poised to lead a research agenda in fiscal year 2013 that will focus not only on basic genome biology and the genomic underpinnings of disease but will also seek to develop strategies for applying genomics to advance medical science and, ultimately, to improve the effectiveness of healthcare.

ENSURING A STRONG FOUNDATION

The unprecedented decreases in the cost of DNA sequencing—resulting from NHGRI-stimulated technology development coupled with myriad innovations by the NHGRI Large-Scale Genome Sequencing Centers—have fundamentally changed how genomic data is now generated as part of biomedical research. Whereas sequencing that first human genome during the Human Genome Project cost upwards of a $1 billion, sequencing a human genome using recently developed technologies will soon cost $1,000 (or less).

The recent renewal of the program supporting the NHGRI Large-Scale Genome Sequencing Centers ensures the productive continuation of flagship initiatives such as The Cancer Genome Atlas (TCGA) in addition to special projects with specialists focusing on specific disorders, such as Alzheimer's disease. These centers will continue to develop innovative methodologies and information management systems, which will inevitably lead to further reductions in the cost of genome sequencing. With such reductions will come the opportunity to sequence the tens of thousands of individual genomes required to understand the small genetic differences that cumulatively confer risk for common diseases, such as diabetes and heart disease. Furthermore, the accessibility of low-cost DNA sequencing technologies will be essential for making genome sequencing a routine part of clinical care.

To facilitate the utilization of genomic tools and information for exploring biological questions and ultimately improving clinical care, the NHGRI Centers of Excellence in Genomic Science will conduct interdisciplinary research and training initiatives focused on the production, analysis, and utilization of genomic data. From these efforts, new insights into the complexity of human genome function are emerging, and these in turn are benefiting the research community at large. Similarly, the human-centric ENCyclopedia of DNA Elements (ENCODE) project and the companion model organism ENCODE project (modENCODE) will continue to build a "knowledge base" that details the functional genomic elements underlying biological processes in humans as well as organisms that serve as important models for studying human biology.

To complement the requisite understanding of normal genome function established by these projects, tools for defining the genetic contributions to human disease are being developed. NHGRI continues to lead efforts within the international 1000 Genomes project to build a deep catalog of genomic variants among different human populations; in turn, this information will be used to identify the subsets of rare and common variants that confer risk for (or protection from) specific diseases or adverse drug responses. Fiscal year 2013 will also see the key maturation of the Human Heredity and Health in Africa (H3Africa) initiative, an NIH Common Fund project managed by NHGRI. The increased knowledge generated about genomic variation and the complex interactions between environmental and genetic factors in African populations will enhance understanding of disease predispositions and drug responses for all human populations.

If genomics is to be a powerful contributor to studies being performed across the biomedical research community, researchers must be able to process and analyze the massive amounts of genomic data that they can now readily produce. NHGRI will pursue the establishment of pioneering approaches for data management and analysis via the development and refinement of bioinformatic tools, resources, and standards.

TRANSLATING THE POTENTIAL

The Genome Sequencing Program continues to be a prominent and vibrant part of the Institute's research portfolio. Looking ahead, it will play an increased role in translating genomic-based capabilities to understand disease biology. The Program's renewal in fiscal year 2012 included not only continued support for medical sequencing projects but also a charge to conduct collaborative research projects with other investigators to broaden the application of genome sequencing as a tool for unraveling the genomic basis of human disease. The prototype for the latter is TCGA, a collaboration with the National Cancer Institute to identify the genomic basis of many different forms of human cancer.

The renewal of NHGRI's Genome Sequencing Program also included establishment of new Mendelian Disorders Genome Centers focused on rare, single-gene (called Mendelian) diseases. These new centers will seek to establish the genetic basis for thousands of rare disorders (affecting millions of Americans) for which the genetic defects remain unknown. Recent advances in genome sequencing offer the hope that the genetic underpinnings for most of these rare diseases can be identified through focused research efforts that were not possible or affordable with previous genome sequencing technologies.

PREPARING FOR GENOMIC MEDICINE

To capitalize on its growing foundation of basic and translational research, NHGRI recently launched the Clinical Sequencing Exploratory Research projects, a new component of the Institute's Genome Sequencing Program. The new projects will investigate how to utilize genomic knowledge in medical settings and begin to explore how healthcare professionals can routinely use genome sequence information for patient care. A related effort, the Electronic Medical Records and Genomics (eMERGE) Network, is pursuing how patients' genomic information can be linked to disease characteristics and symptoms in their electronic medical records, providing the ability to explore associations with disease pathologies and eventually to improve patient care.

Key to the ultimate success in all of these endeavors will be continued attention to the societal implications of advancing genomic technologies and understanding. Deliberate, ongoing engagement by laboratory, clinical, and social scientists and scholars in ethics, law, and philosophy with the public must remain a priority.

Through its portfolio of basic and translational research, the Institute is pushing forward the boundaries of our knowledge and defining the issues that must be addressed before genomics is routinely deployed as a standard element in medical care. NHGRI is leading this charge by funding ambitious research programs to understand the structure and function of genomes more fully, to use genomics as a central tool for understanding the biology of disease, and to establish the path for the implementation of genomic medicine. In all of these pursuits, the Institute maintains a laser-like focus on its ultimate mission—to improve human health through genomics research.

PREPARED STATEMENT OF JUDITH H. GREENBERG, PH.D., ACTING DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget for the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH). The fiscal year 2013 budget of $2,378,835,000 includes a decrease of $48,354,000 less than the comparable fiscal year 2012 level of $2,427,189,000.

This year, in 2012, the National Institute of General Medical Sciences (NIGMS) celebrates its 50-year anniversary as NIH's "basic research institute." Since 1962, NIGMS has continuously supported highly creative people committed to building a broad and deep foundation of discovery. The findings are used and applied by scientists everywhere, leading to new diagnostics, new therapies, and new ways to prevent a wide range of diseases.

MODEL SYSTEMS ILLUMINATE HUMAN HEALTH

Laboratory-animal versions of disease are a staple of basic biomedical and behavioral research. Because fruit flies, worms, mice, and other animals are easy and relatively inexpensive to work with—and have most of the same genes and many of the same behaviors as we do—they are valuable tools for biomedical discovery. Sometimes, though, results with animal models do not hold up in human studies, in part because organisms studied in the laboratory lack the genetic diversity of people. NIGMS has addressed this problem through its support of the Collaborative Cross, a large-scale mouse-breeding project that significantly expands the genetic diversity of mice. This project has made its resources widely available to scientists everywhere—helping to fast-track important discoveries about genetics and human disease.

Other recent studies with model systems, in this case worms, have pointed to new information about a group of neurological diseases that have a common molecular defect: the inability of normal cellular proteins to fold themselves into their proper three-dimensional shapes. Misfolded proteins are implicated in Alzheimer's, Parkinson's, and Huntington's diseases, amyotrophic lateral sclerosis, cancer, cystic fibrosis, and type 2 diabetes. The recent work identified new genes and signaling pathways that keep proteins folded properly and prevent toxic clumping. The researchers also extended their findings by identifying small molecules that appear to repair misfolded proteins.

ALL SYSTEMS GO

While animal models offer key clues to understanding human disease, other studies that investigate large, interacting systems are an essential avenue for learning about health and disease. Systems biology approaches, which promote a more thor-

ough grasp of the intricate and dynamic workings of how molecular and cellular parts interact to make a whole, is a robust area of NIGMS-funded biomedical research.

Human behavior is one example of an enormously complicated system—not just for an individual but also between individuals and within and between populations. Systems biology research employing mathematical models can draw connections among a vast number of inputs, uncovering new connections and making new predictions. NIGMS has joined forces with the NIH Office of Behavioral and Social Sciences Research to identify opportunities, challenges, and gaps in knowledge needed to develop useful models of social behavior. This past fall, NIGMS issued a call for funding research that models social behavior. The new program has generated substantial interest in the research community, and the Institute is looking forward to the results that are likely to have broad application.

Another scientific area of great complexity, even though the subject of study is microscopic, is the interactions between viruses and their hosts. For many years, NIGMS has funded the AIDS-Related Structural Biology Program to obtain the three-dimensional structures of HIV proteins. Representing the culmination of hundreds of studies, researchers have just published a map of nearly 500 physical interactions between components of HIV and those in human cells. The research provides a gold mine for further studies into new drugs and vaccines against HIV.

ACCELERATING THE PACE OF DISCOVERY

As our world has flattened due to increased human travel and expanded commercial trade among many international partners, a number of new diseases have emerged and infected people around the world. To help the Nation and the world understand and prepare for contagious outbreaks, NIGMS funds the Models of Infectious Disease Agent Study (MIDAS). This international effort continues to add new research expertise to increase its capacity to simulate disease spread, evaluate different intervention strategies, and help inform public health officials and policymakers. In 2011, MIDAS scientists used whole-genome sequencing to trace the path of the E. coli outbreak that made thousands of people ill and killed more than 50 people in Germany and France. The project demonstrates the power of modeling and is one of the first uses of genetic detective work to study the dynamics of a foodborne outbreak.

The NIGMS investment accelerates the pace of discovery through its support of chemistry projects that enable biologists to study cells and organisms using state-of-the-art chemical tools; help clarify the chemical reactions that underlie human metabolism; and provide new strategies for drug development. NIGMS-supported chemists recently made two new discoveries that should enhance the manufacture of key drugs. In the first study, scientists made significant progress toward a simpler, more efficient way to synthesize Taxol, an important cancer drug used routinely to treat ovarian, breast, lung, liver, and other cancers. In a second study, NIGMS-funded chemists unveiled the working parts of the commonly used antifungal medicine amphotericin B, nicknamed by physicians "ampho-terrible" for its harsh side effects. The new work opens up possibilities for designing similar antifungal medicines that are just as effective but easier on the body.

INVESTING IN THE FUTURE OF DISCOVERY

The Institute believes that a strong biomedical research workforce is essential for the tandem goals of improving health and maintaining global competitiveness. In 2011, NIGMS published "Investing in the Future: the NIGMS Strategic Plan for Biomedical and Behavioral Research Training." Implementation of this plan is now in full swing. Going forward, NIGMS has articulated clearly that research training is a partnership between the NIH and the academic community and continues to engage actively with its full range of stakeholders. Key foci include the importance of excellent mentoring, a continuing emphasis on diversity, and the need to recognize a full menu of career options beyond academic research for newly trained scientists.

NIGMS has also recently established a new organizational component, the Division of Training, Workforce Development, and Diversity, which integrates training, diversity, and capacity-building activities across Institute programs. This new component also oversees the Institutional Development Award (IDeA) program that broadens the geographic distribution of NIH funding. A new component of this effort is the IDeA Program Infrastructure for Clinical and Translational Research initiative, which encourages applications from IDeA States to develop infrastructure and capacity to conduct clinical and translational research on diseases that affect medi-

cally underserved populations and/or diseases prevalent in these 23 States and territories traditionally underfunded by the NIH.

EXTENDING THE REACH OF BASIC RESEARCH

Within the clinical realm, NIGMS continues to support the NIH Pharmacogenetics Research Network (PGRN), now in its 12th year of funding. This endeavor has yielded a bounty of medically relevant knowledge, including how genetic information can help predict how heart drugs, cancer medicines, nicotine patches, and a range of other treatments are likely to work in a particular person. One PGRN project is now partnering with the Electronic Medical Records and Genomics (eMERGE) Consortium to test samples from people whose electronic medical records are also available to the researchers. The goal is to demonstrate that DNA differences can be useful for decisionmaking about drug type and dosage, and ultimately to improve medication safety and efficacy.

PREPARED STATEMENT OF ALAN E. GUTTMACHER, M.D., DIRECTOR, EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Mr. Chairman and members of the subcommittee: I am pleased to present the fiscal year 2013 President's budget request for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of $1,320,600,000. This reflects an increase of $775,000 more than the comparable fiscal year 2012 level of $1,319,825,000.

50 YEARS OF CONTRIBUTIONS TO HEALTH

This year marks the 50th anniversary of the founding of the NICHD. Thanks to continuing congressional support and the unwavering dedication of our scientists and stakeholders, NICHD research has changed the lives of women, children, families, and those individuals with disabilities worldwide. Since the NICHD was established in the early 1960s, research supported by the Institute contributed to a 50 percent drop in sudden infant death syndrome (SIDS), and a 70-percent drop in respiratory distress syndrome, both leading causes of the Nation's infant mortality rate. Transmission of HIV from infected mother to fetus dropped from 25 percent to less than 1 percent in the past 15 years. Discovery of an early biological marker of pregnancy led to the development of what is now the standard pregnancy test. The incidence of Haemophilus influenzae type b (Hib) meningitis, once the leading cause of acquired intellectual disability, has dropped more than 90 percent with the development of the Hib vaccine by NICHD scientists. Beyond these past contributions to public health, our anniversary presents a unique opportunity to catalyze scientific advances.

NEW ADVANCES CONTINUE THE MOMENTUM

The NICHD's basic research, conducted on the NIH campus and supported at academic institutions nationwide, adds to scientific knowledge and enables clinical researchers to develop and test new treatments. For example, in type 1 diabetes, the immune system destroys the body's insulin-producing cells that help control blood glucose levels. Infertility researchers funded by the NICHD found a way to convert endometrial stem cells into insulin-producing cells and transplant them into mice to control diabetes. These findings suggest that ultimately, a woman's own, readily available, endometrial stem cells could be used to develop insulin-producing islet cells, minimizing the chance of rejection posed by using tissues or cells from another person.

Research shows promise for developing new treatments for uterine fibroids. These noncancerous tumors, 3 to 4 times more common in African American than white women, are often associated with chronic pain, infertility, and preterm labor. Currently, few treatment options exist except surgical removal of the uterus (hysterectomy). A recent NICHD-sponsored analysis concluded that the economic costs of the poor health outcomes, treatment, and management of fibroids in the U.S. may reach $34 billion annually. Other NICHD-supported researchers found that treatment with vitamin D reduced the size of uterine fibroids in laboratory rats predisposed to developing the tumors, suggesting that differential rates of vitamin D deficiency could help explain the health disparities in fibroid formation. Another approach, using a drug to shrink the tumors, has shown promise in preliminary clinical studies.

New technologies and tools are allowing the research community to move science along faster than ever. For example, a NICHD-supported physiatrist is combining

bioengineering with a technique called "targeted muscle reinnervation," using nerves that remain after amputation to control assistive devices; this has enabled researchers to link an individual's brain impulses to a computer in a prosthesis that directs motors to move the limb. The NICHD Small Business Innovation Research (SBIR) program has supported development of emerging technologies to address mounting concerns about the effects of concussions. Scientists have created a device mounted inside a football helmet to measure the impact of a collision. This new tool has already helped to quantify the impact of concussions for college football players, determine how head injuries may differ for football players at different positions, and can be used to design more protective helmets.

Scientists at the NIH's Autism Centers of Excellence are taking advantage of new insights into brain structure and function in their Infant Brain Imaging Study. Using a special imaging technique, they tracked the brain development of infants and toddlers who have an older sibling with an autism spectrum disorder (ASD), and thus, are at increased risk of developing ASD themselves. The researchers found distinctly different patterns of brain development in the younger siblings who were later diagnosed with ASD compared to those who weren't. These findings represent the earliest age (6 to 24 months) at which such biomarkers for ASD have been identified.

It is especially gratifying when scientific advances like these are put into practice. Last year, I reported on a major new study supported by the NICHD demonstrating that fetal surgery to correct myelomeningocele (spina bifida) greatly reduced the risk of death and doubled the chances of children being able to walk, compared to the standard practice of postnatal surgery. Over the past year, the NICHD has convened a series of meetings with numerous leading professional societies to ensure sufficient and consistent training and guidelines for performing this highly complex procedure as it becomes available in various sites around the country.

In late 2011, an NICHD-supported analysis of more than 5 million medical records showed that pregnant women assaulted by an intimate partner are at increased risk of giving birth to infants at lower birth weights. Babies born at low birth weights are at higher risk for SIDS, heart and breathing problems, and learning disabilities. The American College of Obstetricians and Gynecologists used this information in developing physician training materials for screening patients for intimate partner violence.

Since 2002, the NICHD has led the NIH's implementation of the Best Pharmaceuticals for Children Act, supporting pharmacokinetic research and new clinical trials on drugs not previously tested for pediatric use. Due in large part to the NICHD's Pediatric Trials Network, data on pediatric safety, dosing, and efficacy for several common drugs were sent to the Food and Drug Administration this year so that the drugs' labels can be changed, and the children potentially benefiting from these therapeutics can be treated appropriately.

LOOKING AHEAD: SCIENTIFIC VISIONING

As exciting as these advances are, we know that the promise of improving the Nation's health depends on enlightened management of the research enterprise. The NICHD has just concluded a "visioning" process to help us focus over the next 10 years on the best ways to achieve scientific goals, enhance prevention, and continue to improve the Nation's health. After in-depth consultation with more than 700 experts from around the country, white papers covering nine major areas of our science were made available online (http://www.nichd.nih.gov/vision), and a scientific commentary summarizing NICHD's overall vision will appear in a major medical journal later this year. Now the NICHD looks to the future, where we will work with our research partners to detail how genes, the environment, and behaviors interact, starting before birth, to affect health outcomes. We plan to determine all the causes of preterm birth, devise new treatments to maximize gynecologic health, and improve the health and functioning of individuals with intellectual, developmental, or physical differences. Collaborative efforts to strengthen transdisciplinary research and enhance the ways that we conduct science will be essential to this future.

CONCLUSION

Whether they work at the NIH or receive grants at academic institutions across the country, NICHD-supported scientists are an invaluable national resource. In the past year alone, two long-time NICHD grantees were among only seven researchers named by President Obama as recipients of the National Medal of Science. And, to honor her work encouraging young women from the inner city to engage in scientific research careers, a third NICHD grantee was recently awarded the Presidential

Award for Excellence in Science, Mathematics, and Engineering Mentoring. It is with the help of exceptional individuals such as these, and your support, that we will embark on the next 50 years of the NICHD's "Research for a Lifetime."

PREPARED STATEMENT OF STEPHEN I. KATZ, M.D., PH.D., DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH). The fiscal year 2013 NIAMS budget of $535,610,000 includes an increase of $462,000 more than the comparable fiscal year 2012 level of $535,148,000.

INTRODUCTION

As the primary Federal agency for supporting medical research on diseases of the bones, joints, muscles, and skin, NIAMS touches the lives of nearly every American. Training the basic and clinical scientists who carry out this research, and disseminating information on research progress in these diseases, are two other important components of the NIAMS mission.

USING SCIENCE TO INFORM HEALTHCARE DECISIONS

Over the past two decades, the NIH Study of Osteoporotic Fractures (SOF) has provided information that healthcare providers are using to assess people's bone health. SOF's finding that bone mineral density (BMD) relates closely to fracture risk, for example, contributed to Medicare's decision to pay for numerous people to get their BMD measured every 2 years. Many started taking bone-preserving drugs because of their results, and the rate of hip fractures dropped nearly 25 percent among female beneficiaries. New, longer-term data from SOF could refine the screening guidance: women at the highest risk of osteoporosis might benefit from annual exams, while frequent measurements may be unnecessary for others. In fact, women with the lowest risk could be tested much less frequently unless other aspects of their health change.

As multiple treatments become available for various conditions, research is needed to help clinicians decide which options are best for their patients. Studies of adults who have rheumatoid arthritis (RA) suggest that aggressive treatment is more beneficial than waiting until the disease progresses. A group of rheumatologists tested whether a similar approach would reduce the disability and healthcare costs of juvenile idiopathic arthritis (JIA). They compared two therapies and determined that early treatment with either strategy increased the likelihood that the joint-destroying processes would stop.

Many diseases within the NIAMS mission involve pain, fatigue, and other difficult-to-measure symptoms. The ability to quantify changes in these parameters could enhance clinical outcomes research and, ultimately, clinical practice. NIAMS is one of several NIH components engaged in the Patient-Reported Outcomes Measurement Information System (PROMIS) Initiative to develop such a tool. In addition to managing PROMIS on behalf of NIH, NIAMS is encouraging researchers to use the resource in ongoing clinical studies of rheumatic, musculoskeletal, and skin diseases.

For the past decade, researchers have been monitoring the health of people who have low back pain due to intervertebral disk herniation, lumbar spinal stenosis, or degenerative spondylolisthesis. Early findings showed that, in general, most surgical patients fared better than patients who received nonoperative care, although many patients got better without surgery. Recent data show that the cost-effectiveness of surgery for low back pain due to these disorders—4 years after an operation—is comparable to that of other common treatments for nonmusculoskeletal conditions.

Community engagement is a key component for translating interventions into healthcare and integrating lifestyle changes into daily living. To address the well-documented disparities in medical knowledge and research participation, NIAMS will continue its Multicultural Outreach Initiative to improve access to health information for underserved minority populations. Fiscal year 2013 plans include field testing program materials and creating an electronic toolkit to facilitate their dissemination.

INVESTING IN BASIC RESEARCH

Itch is an often difficult and sometimes debilitating symptom of many skin diseases and other disorders within the NIAMS mission. Poor knowledge of the mechanisms underlying chronic itch has hampered the development of pharmacologic treatments. In fiscal year 2013, NIAMS will encourage basic and translational studies in this area.

NIAMS maintains a considerable investment into the genetic and cellular basis of osteoarthritis (OA), with the goal of identifying potential targets for therapies that halt tissue degeneration. Even after researchers develop treatments to stop or reverse OA progression, however, some patients will require total joint replacement. With support from the American Recovery and Reinvestment Act of 2009, researchers made a surprising discovery about the lubricating layer that forms around metal-on-metal hip implants. Instead of cell-based fluid made by the patient, the lubricant is a synthetic material produced through friction. This finding could lead to longer-lasting materials which, in turn, could improve the surgeries' success and reduce their long-term costs.

With the advent of new laboratory and data mining tools, investigators are making connections among biologic processes and organ systems that previously were viewed independently. For example, researchers are learning that inflammation, which plays an important role in RA and other autoimmune joint diseases, is involved in OA onset and osteoarthritic joint degeneration. Others are exploring how normally harmless microorganisms can lead to RA by causing the immune system to attack healthy tissue.

The technologic advances related to genome-wide analyses have enabled investigators to identify a genetic mutation that causes a rare childhood disease characterized predominantly by inflammation and fat loss. The disorder, named chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), may actually represent a spectrum of diseases that have been described in the literature under a variety of names. More importantly, since no treatment for this disease exists, the findings may have uncovered a possible target for future therapies.

ADVANCING TRANSLATIONAL SCIENCES

NIAMS supports several large programs to encourage teams of translational researchers. In fiscal year 2013, it again will partner with other NIH Institutes to fund applications for the Wellstone Muscular Dystrophy Cooperative Research Centers program. The Centers have facilitated numerous basic discoveries and animal tests since their establishment in 2003. A group of investigators that includes Wellstone researchers recently published preclinical data about small molecules that target the defective RNA that causes myotonic dystrophy type 1. The cell-culture and mouse-model findings have the potential to benefit people who have myotonic dystrophy type 1; their promise also extends to other conditions that might be amenable to RNA-targeted therapies.

NIAMS strengthened its Small Business Innovation Research (SBIR) program in recent years by inviting eligible companies to propose studies on specific topics that complement the Institute's other grants. Results from the targeted efforts include a cell-derived human skin substitute for use in consumer product testing, drug discovery, and toxicity screening. NIAMS will continue to look for opportunities that could benefit from an SBIR focus and will solicit applications as areas are identified.

CONCLUSION

The advances described above are just a few of the contributions that NIAMS-funded investigators have made to save and improve millions of American lives. Collectively, the Institute's research, training, and health information programs have significantly advanced our understanding of how to treat or prevent many common, chronic, costly diseases. Looking forward, this progress will serve as a strong foundation for the future, as the burden that these conditions place on individuals and society is reduced and, over time, eliminated.

PREPARED STATEMENT OF STORY C. LANDIS, PH.D., DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH). The fiscal year 2013 NINDS budget of $1,624,707,000 includes an increase of $278,000 more than the

comparable fiscal year 2012 level of $1,624,429,000. The NINDS mission is to reduce the burden of neurological diseases through research. NIH research has improved the lives of many people with neurological disorders directly and by providing the foundation for private sector research. The American Heart Association (AHA) reported that the stroke death rate decreased by 34.8 percent from 1998 to 2008. Better treatments are available for multiple sclerosis, epilepsy, Parkinson's, and other diseases, and genetics research has led to tests that significantly reduce the time to obtain the correct diagnosis for many rare disorders. Moreover, basic science is driving remarkable opportunities for progress. Paradoxically, however, industry is significantly reducing their investment in research on brain disorders because of the challenges brain diseases present. NINDS supports a spectrum of basic, translational, and clinical research to complement and encourage private sector efforts. Because gaps in basic understanding of the normal brain or disease are most often the cause when progress against neurological disease is not forthcoming, the Institute continues to invest more than one-half of its resources in basic research, for which the NIH role is especially crucial.

ACCELERATING DISCOVERY

Last year, for the first time, researchers provided a molecular diagnosis for a family's inherited disease using whole genome sequencing (WGS). The disease was a type of Charcot Marie Tooth disease, a disorder that affects the body's nerves. This year WGS provided not only a molecular diagnosis but also immediate therapeutic benefit. In this study, twin children had been diagnosed with dopa-responsive dystonia, a movement disorder that reflects a deficiency of the neurotransmitter dopamine. The children's health problems persisted despite treatment with the drug l-dopa, which replenishes dopamine and is usually effective. Once WGS identified the specific gene defect, it became apparent that the neurotransmitter serotonin was also deficient. Boosting serotonin with a readily available drug dramatically improved the children's health. Dozens of studies are now underway using these "next generation" sequencing methods in common and rare neurological diseases. A new "Center without Walls," for example, is bringing the best researchers together, regardless of geography, to apply the new genetics technologies to epilepsy.

Next-generation sequencing is just one of several technologies that are transforming basic and clinical neuroscience. Optogenetics allows precise control of nerve cells' activity by light. Induced pluripotent stem cell (iPSC) methods derive nerve cells from skin cells of patients affected by disease, to enable studies of disease and screening of drugs in a culture dish. NINDS supports extensive iPSC research, including consortia in ALS, Parkinson's, and Huntington's disease. Brain imaging now reveals structure, activity, and chemistry of the living brain in health and disease. Recently, for example, brain imaging provided insights about traumatic brain injuries (TBI) in the military, the lingering effects of concussions in young athletes and new understanding of autism . The NIH Human Connectome Project is an ambitious imaging effort to map the wiring diagram of the entire human brain. NIH encourages sharing of data from the Connectome project, gene studies, iPSC methods, and other research that is producing extraordinary amounts of useful information. A notable recent effort to promote data sharing is a TBI database created jointly by the NIH and the Department of Defense.

TRANSLATING DISCOVERY TO HEALTH

NINDS has a long history of translating scientific advances into better medicine. Rare disease studies, bold new therapeutic strategies, and technology development are examples of translational research in which NINDS plays a key role. Several NINDS programs support translational research. The Anticonvulsant Screening Program (ASP) has contributed to the development of eight epilepsy drugs now on the market. Following an external review completed this year, the ASP will refocus on what most concerns the epilepsy community today—drugs to address treatment-resistant epilepsy and to modify the course and development of the underlying disease. Recent activities in the NINDS Neural Prosthesis Program, which pioneered this entire field, include collaboration with Defense Advanced Research Projects Agency (DARPA) to enhance brain control of an advanced prosthetic arm, and development of an ultrathin flexible brain implant that could one day be used to treat epileptic seizures and other disorders. To exploit opportunities across all neurological disorders, the Cooperative Program in Translational Research, begun in 2002, supports teams of academic and small business investigators to carry out preclinical therapy development. NINDS is now funding two Phase II clinical trials of therapies developed in this program. NINDS is also leading an NIH Blueprint Grant

Challenge to develop truly novel drugs that will transform the treatment of nervous system diseases.

Because candidate therapies for many disorders are emerging, in 2011 NINDS launched the NeuroNext clinical network at 25 sites across the United States. NeuroNext will remove roadblocks to the crucial early stage clinical testing of novel therapies and reduce from years to months the time to move new therapies into testing in patients. NeuroNext will test biomarkers for spinal muscular atrophy (SMA) in its first clinical study to prepare for trials of candidate therapies for SMA.

NINDS phase III, multi-center clinical trials continue to advance public health. The Neurological Emergency Treatment Trials (NETT) network completed the Rapid Anticonvulsant Medication Prior to Arrival (RAMPART) trial well ahead of schedule, showing that paramedics in the field can safely deliver the drug midazolam into muscle using an autoinjector (like an EpiPen) and stop continuous seizures faster than the usual intravenous treatment. These results inform responses to common continuous seizures and seizures caused by industrial accidents or nerve agents. NETT trials of stroke and TBI emergency treatments are underway. Also this year, the Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMPRISS) clinical trial showed that patients at high risk for a second stroke who received intensive medical treatment had fewer strokes and deaths than patients who received a stent in blood vessels that supply the brain in addition to the medical treatment. Follow up is continuing to compare longer-term benefits.

With the concern about dementia as our population ages, it is worth noting that stroke is a major contributor to dementia, highlighting the complex relationships among various types of dementia. Not only do the 7 million U.S. stroke survivors have an increased likelihood of cognitive problems, and perhaps also 13 million who have had "silent strokes" but also vascular problems that cause stroke are also associated with Alzheimer's disease. Signs that a stroke has occurred are often found in the brains of Alzheimer's patients, and beta-amyloid, a key protein in Alzheimer's pathology, may stimulate the formation of blood clots, which can cause stroke. Furthermore, last year the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, which is following more than 30,000 people, reported that high blood pressure and other known risk factors for stroke increase the risk of cognitive problems, even among people who have never had a stroke. Research suggests that there is a dementia spectrum from pure vascular dementia to pure Alzheimer's disease, with most patients having contributions from both. Recognition of intersections not only between Alzheimer's disease and stroke but also Alzheimer's disease with TBI, Parkinson's, frontotemporal dementia, and other disorders may provide leads toward better prevention and treatment of all dementias.

Hundreds of neurological disorders affect patients, families, and society. The aging population, concern about the long lasting effects of TBI, and reduced private sector investment are among several factors that underscore the importance of NINDS funded research. Although neurological disorders present enormous challenges, progress in neuroscience and other areas of research provides exceptional opportunities for the future.

PREPARED STATEMENT OF DONALD A.B. LINDBERG, M.D., DIRECTOR, NATIONAL LIBRARY OF MEDICINE

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Library of Medicine (NLM) of the National Institutes of Health (NIH). The fiscal year 2013 NLM budget of $372,651,000 includes an increase of $7,608,000 more than the comparable fiscal year 2012 level of $365,043,000. Funds have been included to allow the National Center for Biotechnology Information (NCBI) to meet the challenges of collecting, organizing, analyzing, and disseminating the deluge of data emanating from research in molecular biology and genomics.

As the world's largest biomedical library and the producer of internationally trusted electronic information services, NLM delivers trillions of bytes of scientific data and health information to millions of users every day. Many searches that begin in Google or a mobile "app" actually retrieve information from an NLM Web site. After 175 years, NLM is a key link in the chain that makes biomedical research results—DNA sequences, clinical trials data, toxicology and environmental health data, published articles, and consumer health information—readily available to scientists, health professionals, and the public. A leader in biomedical informatics and information technology, NLM also conducts and supports leading-edge research and devel-

opment in electronic health records, clinical decision support, information retrieval, imaging, computational biology, telecommunications, and disaster response.

NLM's programs and services directly support NIH's four key initiatives in basic research, technology, translational science, and research training. The Library organizes and provides access to the published medical literature and massive amounts of scientific data from high throughput sequencing; assembles data about small molecules to support research and therapeutic discovery; provides the world's largest clinical trials registry and results database; and is the definitive source of published evidence for healthcare decisions. Research supported or conducted by NLM underpins today's electronic health record systems. The Library has been the principal funder of university-based informatics research training for 40 years, supporting the development of today's leaders in informatics research and health information technology. NLM's databases and its partnership with the Nation's health sciences libraries deliver research results wherever they can fuel discovery and support health decisionmaking.

RESEARCH INFORMATION RESOURCES

NLM's PubMed/MEDLINE database is the world's gateway to research results published in the biomedical literature, linking to full-text articles in PubMed Central, including those deposited under the NIH Public Access Policy, and on publishers' Web sites, as well as connecting to vast collections of scientific data. Through its NCBI, NLM is a hub for the international exchange and use of molecular biology and genomic information, with many databases fundamental to the identification of important associations between genes and disease and to the translation of new knowledge into better diagnoses and treatments. Resources such as dbGaP, the Genetic Testing Registry (GTR) and the ClinVar database create a bridge between basic research and clinical applications.

NLM also stands at the center of international exchange of data about clinical research studies. NLM's Lister Hill National Center for Biomedical Communications builds ClinicalTrials.gov, the world's most comprehensive clinical trials database, including registration data for more than 117,000 clinical studies with sites in 178 countries. ClinicalTrials.gov has novel and flexible mechanisms that enable submission of summary results data for clinical trials subject to the Food and Drug Administration Amendments Act of 2007. To date, summary results are available for more than 5,000 completed trials of FDA-approved drugs, biological products, and devices—providing a new and growing source of evidence on efficacy and comparative effectiveness. NLM is a primary source for results of comparative effectiveness research, providing access to evidence on best practices to improve patient safety and healthcare quality. In 2011, the Library greatly expanded its collection of full-text guidelines, evidence summaries, and systematic reviews from authoritative agencies and organizations around the world.

HEALTH DATA STANDARDS AND ELECTRONIC HEALTH RECORDS

Electronic health records (EHRs) with advanced decision-support capabilities and connections to relevant health information will be essential to achieving precision medicine and helping Americans manage their own health. For 40 years, NLM has supported seminal research on electronic patient records, clinical decision support, and health information exchange, including concepts and methods now reflected in EHR products and personal health record tools, such as Microsoft Health Vault. As the HHS coordinating body for clinical terminology standards, NLM works closely with the Office of the National Coordinator for Health Information Technology to facilitate adoption and "meaningful use" of EHRs. NLM supports, develops, and disseminates several key data standards now required for U.S. health information exchange. While actively engaged in research on Next Generation EHRs, NLM also produces tools, frequently used subsets of large terminologies, and mappings to help EHR developers and users implement health data standards right now. NLM's MedlinePlus Connect is used in multiple EHR products to provide high quality health information relevant to a patient's specific health conditions, medications, and tests, as present in his or her EHR.

INFORMATION SERVICES FOR THE PUBLIC

This EHR connection builds upon NLM's extensive information services for patients, families and the public. The Library's MedlinePlus Web site provides integrated access to high quality consumer health information produced by all NIH components and HHS agencies, other Federal departments, and authoritative private organizations. It serves as a gateway to specialized NLM information sources for consumers, such as the Genetic Home Reference and the Household Products Data-

base. Available in English and Spanish, with selected information in 40 other languages, MedlinePlus averages well over 750,000 visits per day. Mobile MedlinePlus, also in both English and Spanish, reaches the large and rapidly growing mobile Internet audience.

The NIH MedlinePlus magazine, in English and Spanish, is an outreach effort made possible with support from many parts of NIH and the Friends of the NLM. Distributed free to the public via physician offices, community health centers, libraries and other locations, the magazine reaches a readership of up to 5 million nationwide. Each issue focuses on the latest research results, clinical trials and guidelines from the 27 NIH Institutes and Centers.

To be of greatest use to the widest audience, NLM's information services must be known and readily accessible. The Library's outreach program, with a special emphasis on reaching underserved populations, relies heavily on the more than 6,300-member National Network of Libraries of Medicine (NN/LM). The NN/LM is a network of academic health sciences libraries, hospital libraries, public libraries and community-based organizations working to bring the message about NLM's free, high-quality health information resources to communities across the Nation.

DISASTER INFORMATION MANAGEMENT

Through its Disaster Information Management Resource Center, NLM builds on proven emergency backup and response mechanisms within the NN/LM to promote effective use of libraries and information specialists in disaster preparedness and response. NLM conducts research on new methods for sharing health information in emergencies as its contribution to the Bethesda Hospital Emergency Preparedness Partnership, a model of private-public hospital collaboration for coordinated disaster planning. NLM works with the Pan American Health Organization (PAHO) and the Latin American Network for Disaster and Health Information to promote capacity-building in disaster information management. In addition, NLM responds to specific disasters worldwide with specialized information resources appropriate to the need, including a recently launched Disaster Information Apps and Mobile Web Sites page.

In summary, NLM's information services and research programs serve the Nation and the world by supporting scientific discovery, clinical research, education, healthcare delivery, public health response, and the empowerment of people to improve personal health. The Library is committed to the innovative use of computing and communications to enhance public access to the results of biomedical research.

PREPARED STATEMENT OF RODERIC I. PETTIGREW, PH.D., M.D., DIRECTOR, NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health. The fiscal year 2013 NIBIB budget of $336,896,000 is $1,058,000 less than the comparable fiscal year 2012 level of $337,954,000.

The mission of NIBIB is to improve human health by leading the development and accelerating the application of biomedical technologies. NIBIB invests resources in scientific and technological research opportunities at the convergence of the physical, quantitative and life sciences, and in training the next generation of researchers. The Institute is at the forefront of translating scientific advances into engineered medical solutions. Ultimately, NIBIB seeks to realize innovations that address healthcare challenges, reduce disease mortality and morbidity, and enhance quality of life. To accomplish this goal, NIBIB continues to fund bold and far-reaching projects that facilitate discovery and translate basic science into better healthcare.

DISCOVERY SCIENCE AND TECHNOLOGIES TO EMPOWER PATIENTS

Neurostimulation Research in Paraplegics: Recovery of Voluntary Motion, Bladder, and Sexual Function.—Through the NIBIB Rehabilitation Engineering program, researchers from the University of California, Los Angeles, have developed a high-density electrode array technology for epidural stimulation of the spinal cord. The first patient, the victim of a car accident that left him completely paralyzed from the chest down, received electrical stimulator implants in his lower back. Over a 1-year period, he received daily electrode stimulating sessions with specific tasks and movements being performed, which is known as locomotor training. The procedure resulted in independent standing, some voluntary leg control, and regained bladder,

bowel, and sexual function. It is believed that the epidural stimulation and locomotor training have two distinct roles. The stimulation appears to switch on intact circuits in the spinal cord, while the training relays specific information about body and limb positions. The investigators have applied this technology to three patients with complete spinal cord injury. All patients are able to stand and voluntarily control both legs in the presence of epidural stimulation.

Wireless Tongue Drive System Could Provide Independence to Paralyzed Patients.—Assistive technologies (ATs) have been available to control devices used for daily living such as powered wheelchairs and computers. However, many of these devices have limited commands, cause rapid muscle fatigue, or interfere with the user's basic functions. NIBIB-funded researchers from the Georgia Institute of Technology have developed a tongue-operated AT called the Tongue Drive System (TDS) that is unobtrusive, wearable, wireless, and can substitute for many arm and hand functions. The core TDS technology exploits the fact that even a person with severe paralysis that impairs breathing and speech can still move their tongue and therefore, can fully utilize this extraordinary system. The device consists of a headset, a compact computer, and a tiny magnet attached to the tongue. Tongue movements change the magnetic field around the mouth. These changes are detected by magnetic sensors in the headset, relayed to the computer, and translated into the commands of the user. The system allows users to control various devices and perform numerous tasks such as drive their wheelchairs, operate their computers, and generally control their environment in an independent fashion. The TDS can be linked to currently available technologies such as a smart phone, to control household appliances, lights, locks, heating/air conditioning, as well as prosthetic arms or legs. This remarkable technology could offer paralyzed individuals an unprecedented level of independence for leading active, productive lives.

TECHNOLOGIES TO ACCELERATE THERAPEUTICS DEVELOPMENT

Multi-Layered Nanoparticles for Specific Delivery of Drugs to Tumors.—An important area of investigation supported by NIBIB is targeted drug delivery, e.g., to cancer cells and not the surrounding normal tissue. One group of investigators has created multilayered nanoparticles that can be delivered systemically (by venous injection) but act only at the site of the tumor due to the specific chemical properties of each layer and their interaction with the specific biochemistry of tumor cells. The properties of the outer surface layer were designed to provide a surface that promotes distribution of particles throughout the body and shields the drug while preventing binding to healthy tissues. This outer "stealth" layer is also pH-sensitive and is shed in the acidic environment of tumors exposing the toxic load of the nanoparticle. At the site of a tumor, the shed surface layer reveals a charged nanoparticle layer, which contains the anti-cancer agent and is readily taken up by tumor cells. The investigators have demonstrated that this concept for tumor targeting is applicable to a broad range of cancers and compatible with various therapies designed to be triggered by acidic tumor tissue. Because particles can be designed with layers that can be shed in specific environments, the cancer drug can be exposed and delivered directly to the tumor, which makes this emerging technology an extremely promising cancer drug delivery technique.

Nanoscale Theranostics: Delivering Treatment and Monitoring Efficacy Simultaneously.—Recent advances in nanoscience have spurred new developments in the field of theranostics (the combination of both therapeutic and diagnostic functions in a single system). These integrated systems have been shown to selectively transport therapeutic agents to target tissues while simultaneously monitoring biological responses to the delivered therapy. The current challenge is to develop systems or "platforms" that allow the optimization of the function of each of the combined molecular components that target the disease site, deliver the therapy, and allow for imaging of the results immediately. Researchers recently developed a nanoscale delivery platform known as polymer-caged nanobins (PCNs). The surface of PCNs can be chemically modified to attach a variety of molecules in order to target specific cells or tissues. The platform is liposome based, which allows for a simplified loading and encapsulation of a range of therapeutic drugs. To allow monitoring of the response to therapy, the PCN shell contains magnetic resonance imaging (MRI) contrast agents, which provide images of the drug targets as well as real time images of the response to the drug, e.g., reduction in tumor size. This type of theranostic can make the treatment of numerous diseases safer and more successful because the prescribed regimens can be adjusted in real time during treatment.

ACCELERATING EARLY DIAGNOSIS AT THE POINT-OF-CARE

Handheld Nuclear Magnetic Resonance for Rapid Point-of-Care Diagnostics.—One of the major challenges in medicine is the rapid and accurate measurement of proteins that are biomarkers of a specific disease, or pathogens in biological samples. Magnetic particles which target biomarkers are attractive candidates for such biosensing applications because most biological samples do not have any background magnetization that would interfere with detection. A handheld micro-nuclear magnetic resonance (NMR) device, which can detect such particles, has recently been developed for rapid approximately one-half hour analysis of a variety of biologics, from bacteria identification in small fluid samples to protein markers of cancer. The device employs magnetic particles that bind to targets of interest, creating a signal detectable by the micro-NMR. Also known as diagnostic magnetic resonance (DMR), this powerful biosensor technology offers unique advantages, such as robust signal amplification, broad applicability to profile different types of targets (DNA, proteins, metabolites, and cells), minimal sample preparation, ability to perform measurements in turbid media, and high-throughput capacity. Importantly, the low cost and ability to use the device at the point-of-care could make important contributions to the battle against serious public health issues such as tuberculosis and HIV in underserved populations. In an early study of patients with unknown solid masses, the diagnosis of cancer was made at the bedside in approximately one-half hour and with higher accuracy than with the traditional method of tissue biopsy which requires two days for final results.

NEW INVESTIGATORS, NEW IDEAS

NIBIB Design by Biomedical Undergraduate Teams Challenge.—The Design by Biomedical Undergraduate Teams (DEBUT) challenge is a new NIBIB program opened to teams of undergraduate students working on projects that develop innovative solutions to unmet health and clinical problems. The main goals of the challenge are:

—to provide undergraduate students experience in working in teams to identify unmet clinical needs, and design, build and debug solutions for open-ended problems;
—to generate novel, innovative tools to improve healthcare, consistent with NIBIB's mission; and
—to highlight and acknowledge the contributions and accomplishments of undergraduate students.

Entries have been solicited in three categories:

—Diagnostic Devices and Methods;
—Therapeutic Devices and Methods; and
—Technologies to Aid Underserved Populations and Individuals with Disabilities.

The winning student team in each category will receive a $10,000 prize at the NIBIB DEBUT Award Ceremony during the annual conference of the Biomedical Engineering Society.

PREPARED STATEMENT OF JOHN RUFFIN, PH.D., DIRECTOR, NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Institute on Minority Health and Health Disparities (NIMHD) of the National Institutes of Health. The fiscal year 2013 NIMHD budget of $279,389,000 includes an increase of $3,278,000 more than the comparable fiscal year 2012 level of $276,111,000.

INTRODUCTION

Millions of Americans from racial and ethnic minority, rural and low-income populations continue to be burdened by disparities in health status and healthcare, despite recent scientific and medical advances to improve the quality of health in this nation. Evidence-based research has shown that these disparities result from the interaction of multiple chronic influences, such as social, environmental, behavioral, and biological factors. Traditionally, research emphasis has been on examining the biology of health disparities. In recent years, the impact of social factors has become more evident in having a strong causal linkage to health disparities. For example, the role of the social and physical environment, the effect of poor housing circumstances, and the difficulties of accessing transportation to obtain timely needed medical care, are all important factors. Therefore, the elimination of health disparities requires a coordinated and integrated approach across multiple disciplines to

understand and solve the underlying biological and nonbiological evolution of health disparities. NIMHD has been at the forefront leading scientific research and building bridges to eliminate health disparities while working with public and private sector partners.

INNOVATION IN RESEARCH

NIMHD administers a portfolio of programs aimed at approaching health disparities from many angles, embodied in the principal goals of research, research capacity building, and outreach. Through research, the NIMHD seeks to understand the development and progression of diseases and conditions disproportionately affecting underserved populations, and to develop evidence-based strategies to improve prevention, diagnosis, and treatment methods. The Centers of Excellence (CoE) Program continues to be a powerful force for encouraging large-scale, transdisciplinary research. CoE researchers have analyzed associations between insulin resistance and other markers of disease in a sample of Mexican-American adolescents from a severely disadvantaged community on the Texas-Mexico border. This study found that approximately 50 percent of their sample (mean age, 16 years old) were overweight or obese, and more participants were obese than overweight. Participants (27 percent) in this sample had insulin resistance, a strong predictor of diabetes, and two biomarkers, low high-density lipoprotein cholesterol and high waist circumference, were strongly linked to insulin resistance. These findings emphasize the need to address insulin resistance at least as early as adolescence to prevent adverse economic, social, and health consequences. Another group found evidence that supports the hypothesis that the loss of function of a molecule that promotes cell adhesion contributes to the development of the aggressive breast cancer commonly found in African-American women. NIMHD COE researchers have also discovered that moral beliefs and lack of awareness contribute to low rates of cervical cancer screening in young Asian-American women.

TOWARD DIVERSITY IN THE WORKFORCE

Building the capacity of individuals, institutions, and communities to conduct research and undertake training, with the goal of strengthening the diversity of the science and medical workforce, are crucial to improving the quality of healthcare of America's underserved populations. The Research Endowment, Research Centers in Minority Institutions (RCMI), and the Building Research Infrastructure and Capacity (BRIC) Programs are the pillar of the NIMHD support for building a national enterprise of academic institutions with the physical and intellectual capability to be leaders in health disparities research. At the University of Texas Brownsville, NIMHD funding has helped to leverage resources for the creation of a new college, the College of Biomedical Sciences and Health Professions, and establish a new degree program in biomedical sciences.

NIMHD continues to recruit an average of 250 new candidates into its Loan Repayment Program annually, adding to the diversity of individuals from health disparity populations in the science and health professions workforce. Many of these scholars are engaged in behavioral, social sciences, prevention, health services, and community-oriented research exploring the various social determinants of health. Some of the innovative research projects include studying text messaging to improve depression treatment adherence in low-income patients, creating web-based treatment programs for substance use in American Indian and Alaska Natives, and examining how perceived discrimination and health system distrust affect behavior and decisionmaking related to cervical cancer prevention in rural and minority women.

ENGAGING COMMUNITIES

Harnessing the power and insights of diverse communities is another important factor because health disparity populations often encounter cultural or environmental barriers to improved health. Outreach efforts remain at the core of the NIMHD's commitment to engage communities in the research process, and equally important, to translate research findings into culturally and linguistically appropriate tools and programs to educate and empower affected communities and their healthcare providers. The Community-Based Participatory Research (CBPR) Initiative supports research that engages communities in the research process as equal partners with scientists. This engagement is valuable in helping communities sustain healthy behaviors over the long-term. For example, one project at Wake Forest University trained members of Latino soccer teams in North Carolina to discuss HIV-prevention behaviors with fellow players. After 18 months, men in the intervention group were significantly more likely to report consistent condom use and

HIV testing than those in a control group. Grantees at Saint Louis University are increasing fruit and vegetable consumption by local black men by producing community gardens. These plots have provided more than 1,800 pounds of fresh produce to 150 families, and residents showed decreases in hypertension and body mass index.

A FUTURE OF SUSTAINABLE COMMITMENT

NIMHD seeks to ensure that the investment and progress that has been made toward eliminating health disparities is not lost. It will continue to identify opportunities to sustain effective programs and initiatives by forging and strengthening partnerships across all sectors, while accelerating the pace of research, policy, practice, and community interventions to address pervasive barriers and emerging issues impeding the elimination of health disparities. It will also be imperative to establish an effective system of coordination for these inter and intra-agency activities. Enhanced understanding of the social determinants of health and how where we live, work, and play influence health outcomes are among the priorities that must be aggressively advanced through innovative approaches. While the issues are many, NIMHD is confident that the infrastructure it has built throughout the Nation is up to the challenge, and it is poised to support and create sustainable interventions that will move the country closer to eliminating health disparities. Ensuring that all Americans have an equal chance at healthy life is not an option. NIMHD remains committed to achieving health equity for underserved communities.

PREPARED STATEMENT OF SUSAN B. SHURIN, M.D., ACTING DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Mr. Chairman and members of the subcommittee: 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 2013 NHLBI budget of $3,076,067,000 includes an increase of $709,000 more than the comparable fiscal year 2012 level of $3,075,358,000.

The NHLBI leads research and education programs to discover and apply knowledge to improve health by preventing and treating heart, lung, and blood diseases. I appreciate the opportunity to highlight just a few examples of our success in doing so and some of our most promising research programs that will enable further advances.

CHRONIC DISEASE RISK REDUCTION

Cardiovascular diseases (CVD) and pulmonary conditions are among the leading causes of disability and death around the world. Although their prevention and treatment have improved dramatically, without further progress they will continue to impose an increasing health burden as our population ages. A recent meta-analysis of lifetime risk for CVD underscored the availability of lifelong opportunities for CVD prevention. The Institute is funding a clinical trial to examine diet and exercise interventions to improve neurocognition in patients with CVD risk factors who have cognitive impairment. Effective ways to help people lose weight and sustain weight loss were identified in an NHLBI-supported study reported in November 2011; multiple ongoing projects are addressing ways to help children and adults in a wide range of circumstances improve their health through weight control and physical activity.

The NHLBI continues to focus upon understanding CVD risk in vulnerable populations. The Jackson Heart Study is addressing the biological, behavioral, and psychosocial factors that account for the high burden of CVD in African Americans. The Hispanic Community Health Study—Study of Latinos is addressing the factors involved in the prevalence and development of CVD in Hispanic populations in the United States. Both studies are expected to be renewed in fiscal year 2013. A new program planned for fiscal year 2013 will foster development of effective and sustainable public health interventions to reduce CVD morbidity and mortality in high-risk rural populations.

INTERPRETING THE HUMAN GENOME IN HEALTH AND DISEASE

Data from the NHLBI's substantial investment in whole exome sequencing of participants in its long-term cohort studies is paying off: data are now being deposited in dbGaP, the informatics resource at the National Library of Medicine, for use by

investigators around the world. The return on this investment will provide valuable new diagnostics and treatments for the next decade.

The NHLBI has led multiple global consortia in sharing data and encouraging analysis of large genomic data sets linked to phenotype. One such consortium identified 16 genetic loci important for control of blood pressure that are now being explored by other NHLBI-supported investigators as new approaches to control blood pressure. Still other NHLBI-supported studies are revealing the genetic and environmental causes of chronic obstructive pulmonary disease (COPD), asthma, abnormalities of heart rhythm, and factors that affect the severity of hemoglobin disorders such as sickle cell disease.

NEW THERAPIES FOR HEART, LUNG, AND BLOOD DISORDERS

The NHLBI supports development of improved therapies for heart disease through resources such as the Cardiac Translational Research Implementation Program (C–TRIP) and their assessment in clinical trials through Institute-initiated programs such as the Pediatric Heart Network (now completing a trial in Marfan's syndrome and multiple studies of genetics and clinical management of congenital heart disease), the Heart Failure Network (conducting studies of cellular and drug therapies of heart failure), and the Cardiothoracic Surgical Trials Network (conducting comparative studies of surgical approaches).

Several NHLBI programs are advancing translation of basic scientific knowledge into new therapies. The Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases (CADET) will accelerate the development of agents for diagnosing and treating lung diseases. Investigators are partnering with other NIH programs such as Therapeutics for Rare and Neglected Diseases (TRND) to do early-stage translational work that will be followed by NHLBI-supported clinical trials.

GENE AND CELLULAR THERAPIES

NHLBI-supported scientists recently reported success in treating hemophilia B, an inherited bleeding disorder, in several patients with a single infusion of a gene therapy that durably boosted the production of the missing clotting factor. If confirmed in other patients, this approach may allow patients to minimize or discontinue expensive treatment with replacement clotting factor.

Encouraging results from studies that use gene therapies in animal models for other diseases offer promise for the treatment of human disease. For example, a unique genetic approach of replacing the single mutated amino acid in mice cured their sickle cell disease. A new form of gene therapy for heart failure improved heart function in pigs without apparent toxicity.

Bone marrow transplantation has been standard clinical therapy for certain diseases since the 1960s. The NHLBI is the primary Institute supporting the Bone Marrow Transplant (BMT) Clinical Trials Network (CTN), with strong support from the NCI. A BMT CTN finding that use of mobilized peripheral blood stem cells rather than bone marrow substantially lowers the risk of graft-versus-host disease (an often fatal complication of BMT) has already affected practice and should lessen complications of BMT.

The NHLBI is supporting resources such as the Production Assistance for Cellular Therapies program to facilitate laboratory and clinical studies of cellular therapies to enhance healing after tissue damage caused by myocardial infarction and some forms of lung disease. Use of mesenchymal stem cells to repair tissue without scarring is being tested in early-stage human trials, with some very encouraging results.

RARE DISEASES

The NHLBI supports infrastructures—registries, clinical trial networks, and biorepositories—to enable research on rare diseases and on risk factors for more common diseases. For example, both sporadic and Marfan-associated thoracic aortic disease may have a common pathway, and a genetic cause of aortic aneurysms may be more prevalent than previously thought. The NHLBI is a leader in conducting clinical trials in pulmonary hypertension and idiopathic pulmonary fibrosis. Linkage of genetic and clinical data with a biorepository is enabling identification of factors influencing the development of congenital heart disease.

Following promising studies in mice, the NHLBI is now completing a study of losartan, an FDA-approved antihypertensive drug, in Marfan syndrome. The NHLBI supported a clinical trial that showed rapamycin (Sirolimus) stabilized lung function, reduced symptoms, and improved quality of life in patients with lymphangioleiomyomatosis (LAM), a progressive cystic lung disease in women. NHLBI partnerships with patient advocacy organizations in the conduct of both trials facilitated their rapid enrollment and completion.

Sickle cell disease remains an area of intensive focus for the NHLBI. A trial recently demonstrated that hydroxyurea, known to be an effective treatment for adults, is also safe and effective in very young children. In fiscal year 2013, the NHLBI plans to initiate Excellence in Hemoglobinopathy Research Awards to promote multidisciplinary basic and translational research and facilitate collaboration with clinical hematologists. The NHLBI has played a major role in a Department of Health and Human Services (HHS)-wide initiative to coordinate the research and healthcare delivery efforts of six HHS components to reduce the health burdens of hemoglobinopathies (sickle cell disease and thalassemia). The NHLBI is developing clinical practice guidelines to ensure that providers know the components of high-quality, evidence-based care for sickle cell disease.

HEMOVIGILANCE

The NHLBI supports multiple studies, and works closely with the FDA, to ensure appropriate monitoring of the blood supply against potential threats. In 2010 and 2011, an NHLBI-led interagency group demonstrated that a xenotropic murine retrovirus (XMRV), which had been reported to be associated with chronic fatigue syndrome in some patients, did not pose a risk to the safety of the blood supply. NHLBI leadership ensured that this and other important health questions were quickly resolved.

PREPARED STATEMENT OF PAUL A. SIEVING, M.D., PH.D., DIRECTOR, NATIONAL EYE INSTITUTE

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Eye Institute (NEI) of the National Institutes of Health (NIH). The fiscal year 2013 NEI budget of $693,015,000 includes a decrease of $8,861,000 less than the comparable fiscal year 2012 level of $701,876,000. As the Director of the NEI, it is my privilege to report on the many research opportunities that exist to reduce the burden of eye disease.

CLINICAL/TRANSLATIONAL RESEARCH

Gene Therapy.—In 2008, NEI-supported investigators reported results from a landmark phase I clinical trial of gene therapy in three patients with a blinding, early onset retinal disease, Leber congenital amaurosis (LCA), which is caused by a defect of the RPE65 gene. Treatment, consisting of injecting a viral vector to deliver normal copies of the RPE65 gene, was well tolerated, and there was objective evidence of modest visual improvement in all three study subjects. To date, 15 participants have been treated and all have experienced visual improvements. Recently published clinical trial results find that increasing the dose with a second injection safely expands the area of retina exposed to the treatment (RPE65–AAV). Responsiveness of light-sensitive photoreceptor cells near injection sites increased after treatment. Younger participants, when compared to older participants, did not experience greater visual improvements. In fact, the two participants with the greatest visual acuity gains were among the oldest in the study. The researchers speculated that the number and health of remaining photoreceptors matter more than patient age, as the rate of photoreceptor loss varies considerably among people with RPE65-deficient LCA. The finding suggests that careful evaluation of photoreceptor cell health is important in determining potential clinical trial participants. Because safety was the primary outcome of this trial, a conservative approach was taken that limited treatment to the eye with poorer vision. In the future, the researchers plan to seek further visual gains by administering three injections of RPE65–AAV and treating the better eye.

A team of NEI investigators restored vision in a canine model of X-linked retinitis pigmentosa (XLRP) using a new gene therapy vector capable of transfecting both rod and cone cells. XLRP is a severe retinal disease that affects both rod and cone photoreceptor cells. Patients with XLRP experience night blindness as children and become blind by middle age. A common form of XLRP results from mutations in the retinitis pigmentosa GTPase regulator (RPGR) gene. Treatment restored lost photoreceptor cell structure and repaired photoreceptor cell connections to other retinal neurons that send visual signals to the brain. This study provides a clearer path to clinical trials for XLRP. In addition, gene therapy trials for age-related macular degeneration (AMD), choroideremia, Leber's hereditary optic neuropathy, Stargardt macular dystrophy (SMD), and Usher syndrome were launched this past year. Clinical trials for juvenile retinoschisis, achromatopsia, and retinitis

pigmentosa are also planned. All of these trials were made possible by sustained NEI support to develop and refine gene therapy techniques.

Stem Cell Therapies.—In January 2012 Advanced Cell Technologies published preliminary results of the first-ever clinical trials of a product derived from human embryonic stem cells (hESCs). These landmark clinical trials are evaluating hESC-derived retinal pigment epithelium (RPE) cells for the treatment of Stargardt's macular dystrophy (SMD) and age-related macular degeneration (AMD). In the two treated patients, there were no adverse events and both had modest but objective improvements in vision. The RPE is a highly specialized layer of cells adjoining the retina that support photoreceptor cell function. SMD and AMD are known to result from a diseased RPE.

GENETICS

NEI created the International AMD Genetics Consortium in 2010 to identify the remaining genetic risk variants for AMD. To increase the statistical power needed to identify genes that have small, yet significant contributions to AMD, the consortium is conducting a meta-analysis on 15 Genome Wide Association Studies (GWAS) representing more than 8,000 patients with AMD and 50,000 controls. In addition to verifying known genes, the consortium identified 19 new gene variants. The genes identified in these studies function in the immune system, cholesterol transport and metabolism, and formation and maintenance of connective tissue. This study provides a nearly complete picture of genetic heritability for AMD. NEI's effort to unite the international research community to share GWAS data sets made it possible to solve a common goal in our understanding of this blinding disease.

In 2009, NEI established the NEI Glaucoma Human Genetics Collaboration (NEIGHBOR), a consortium of clinicians and geneticists at 12 institutions throughout the United States dedicated to identifying the genetics of glaucoma. NEIGHBOR collected and sequenced 6,000 DNA samples and is the largest genetics study of glaucoma. Thus far, NEIGHBOR investigators identified a risk variant in the gene CDKNB2. This gene is thought to play a role in the development of the optic nerve head, where retinal ganglion cell axons, which degenerate in glaucoma, converge to form the optic nerve. NEI will make GWAS data from NEIGHBOR available to the vision research community for further evaluation in 2012.

NEUROSCIENCE

In 2011, NEI awarded a grant to support Project Prakash, which combines an extraordinary scientific opportunity with a humanitarian mission. Understanding how the human brain learns to perceive objects remains a fundamental challenge in neuroscience. Project Prakash seeks to treat older children born with congenital cataracts and other eye disorders and then study how their visual function develops. Visual development normally takes place during infancy before children acquire language and can communicate what they are seeing. By treating older children who can fully communicate, Project Prakash will permit scientists to more directly address the nature of neuroplasticity and visual development. This study will also provide important clinical insights to inform visual rehabilitation. India accounts for nearly 30 percent of the world's blindness. Many are poor children with treatable congenital eye disorders, but most never receive medical attention because they live in rural areas far from urban medical centers. Tragically, it is estimated that 60 percent of India's blind children die before reaching adulthood. Project Prakash is a unique opportunity to offer humanitarian medical aid while advancing the field of neuroscience.

PREPARED STATEMENT OF MARTHA J. SOMERMAN, DDS, PH.D., DIRECTOR, NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health (NIH). The fiscal year 2013 NIDCR budget of $408,212,000 includes a decrease of $2,010,000 less than the comparable fiscal year 2012 level of $410,222,000.

Science long has served as one of the Nation's most essential economic engines. From the Human Genome Project to the Internet, scientists started with basic research questions that later propelled American entrepreneurship into creating previously unimaginable new markets. So what types of research now are advancing in the Nation's laboratories and clinics that might one day propel American industry and public health to new heights? Today, I offer a brief overview of NIDCR's invest-

ment and progress in a few key areas, and suggest their potential to enhance the dental, oral, and craniofacial health of millions of Americans.

CHRONIC INFLAMMATION

A great place to start is with a promising therapeutic approach that mimics the body's own signals to control inflammation and inflammatory pain. Inflammation is part of the immune system's normal response to infections and tissue injury. Without it, tissues would not heal. At some pre-programmed point, when the threat subsides, the response turns off and inflammation is resolved. For millions of people, however, the immune system's signals get crossed and inflammation is dangerously prolonged.

An NIDCR grantee has developed promising candidate compounds based on the body's own inflammation-resolving molecules. The compounds have proven potent at reducing inflammation and inflammatory pain in animals without the adverse side effects of available analgesics. The plan is to move into human studies within the next year to evaluate their safety and efficacy in turning off the destructive inflammation occurring in periodontal disease. The hope is these compounds one day will provide a more effective approach to managing this widespread oral condition and, possibly, other chronic inflammatory conditions elsewhere in the body.

CHRONIC PAIN

The Institute of Medicine reported in 2011 that more than 116 million Americans suffer from chronic pain, with annual costs of approximately $600 million. The profound complexity of the body's processes for perceiving and responding to pain is a key factor contributing to the current inadequacies of chronic pain control and interventions to prevent the transition from acute to chronic pain. For the most part, chronic pain conditions and their molecular underpinnings remain poorly understood. This is changing. In late 2005, NIDCR began supporting the first-ever, large longitudinal clinical study of a chronic pain condition. It focuses on temporomandibular joint and muscle disorders (TMJDs), a common group of conditions that affect the area in and around the jaw joint and often overlap with other chronic pain conditions. Preliminary findings, reported in December 2011, identified mutations in genes linked to chronic TMJD, including genes associated with stress, psychological well-being, and inflammation. Building on this work, NIDCR places a high priority on supporting research on the genetics of chronic orofacial pain, with a focus on identifying gene variants that influence pain perception, their interactions with environmental triggers, and behavioral responses to pain.

In other work, NIDCR-supported behavioral scientists are providing insight into factors influencing providers' treatment decisions for chronic pain. They found that decisions tend to be influenced by individual characteristics of patients, such as gender and race or ethnicity, which are extraneous to the pain condition itself. These results are leading to new ways of training providers, helping to focus treatment decisions on more clinically relevant factors.

ORAL CANCER

Personalized healthcare offers tremendous promise for improving the lives of people diagnosed with cancer, as well as other diseases. Among new cancer occurrences, oral and pharyngeal cancer (OPC) is the eighth most common among U.S. men and seventh among African-American men, affecting more than 30,000 people each year. Since 2009, NIDCR has invested in the Oral Cancer Genome Project, which aims to define the genetic changes driving development of oral and pharyngeal tumors. As part of this project, NIDCR-supported researchers employed next-generation sequencing technology to yield one of the most comprehensive analyses yet of the genetics underlying head and neck squamous cell carcinoma (HNSCC), the most common of OPCs. The genomics data provide evidence that HNSCC involves dozens of distinct molecular conditions, each driven by a unique pattern of gene alterations. NIDCR will support work to validate the research findings, which could help identify and reclassify these tumors based on their individual specific molecular characteristics—a key first step in establishing personalized therapies.

Another important result from the Oral Cancer Genome Project was the confirmation that head and neck tumors associated with human papillomavirus (HPV) infection have their own distinct genetic profile. HPV is associated with a subset of OPCs that increased by 225 percent from 1998 to 2004. NIDCR supports research to understand the natural history of this growing public health issue.

The Institute also supports research to improve the survival rate for HNSCC. In a significant advance, scientists in NIDCR's laboratories demonstrated that metformin, a widely used anti-diabetes drug, prevents development and progression

of oral squamous cell carcinomas in mice. NIDCR is initiating clinical studies to determine its effectiveness in humans, opening a new approach to treating this deadly cancer.

CRANIOFACIAL DEVELOPMENT

Cleft lip and cleft palate (CLP) are among the most common of all birth defects, occurring in 1 of 700 live births in the United States, or 7,000 babies per year. Treatment is expensive and difficult, requiring multiple surgeries, orthodontics, and speech therapy over a period of years. NIDCR takes a multi-pronged approach to these devastating conditions, incorporating basic research with prevention, treatment, and post-treatment research. The goal is fewer children born with CLP, better outcomes for those afflicted with the disorders, and less cost and stress for families.

Through genome-wide studies, NIDCR-supported investigators defined several genetic and environmental CLP risk factors. This work set the stage for a researcher co-funded by NIDCR and NICHD to develop a mouse model that closely mimics CLP. The same researcher demonstrated that restoring function in one molecule resulted in complete correction of a cleft lip defect in mouse embryos still developing in utero.

NIDCR-funded investigators have found that many children born with CLP have impaired cognitive functioning that goes undetected until the child is older and remediation is more difficult. Early screening for cognitive deficits in children with CLP may help them reach their full potential through timely, tailored instruction. Research on early screening technologies is underway. In addition, NIDCR continues to fund research to optimize care for children with clefting disorders, including clinical studies comparing the cost and effectiveness of intervention procedures.

NIDCR's investment in small business innovation research (SBIR) and small business technology transfer (STTR) programs is sparking economic activity and improving outcomes for people with craniofacial defects such as CLP. An NIDCR grantee developed surgical simulation software to help clinicians plan and optimize craniofacial surgery and provide a 3D prediction of patients' outcomes. Another grantee leveraged SBIR/STTR investments to patent a minimally invasive surgical instrument system to aid periodontal surgery, often needed by people with CLP.

EVIDENCE-BASED CARE

NIDCR efforts to strengthen the knowledge base for dental practice will accelerate in April 2012 with the establishment of a National Dental Practice-Based Research Network. Building on the success of precursor regional networks, the national network will leverage the power of large numbers of practitioners to propose and perform clinical studies on topics important to dentistry. Because the research is conducted in the real-world environment of dental practice, dentists are more likely to accept and adopt the findings. The expected result is nothing short of a transformation of dental practice—one that will result in more individualized and evidence-based treatment and prevention, to the benefit of millions of Americans.

PREPARED STATEMENT OF LAWRENCE A. TABAK, D.D.S., PH.D., PRINCIPAL DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the Office of the Director (OD) of the National Institutes of Health (NIH). The fiscal year 2013 OD budget of $1,429,161,000 includes a decrease of $28,220,000 less than the comparable fiscal year 2012 level of $1,457,381,000.

The OD promotes and fosters NIH research and research training efforts in the prevention and treatment of disease through the policy oversight of both the extramural grant and contract award functions and the Intramural Research program. The OD stimulates specific areas of research to complement the ongoing efforts of the Institutes and Centers through the activities of several cross-cutting program offices. The OD also develops policies in response to emerging scientific opportunities employing ethical and legal considerations; provides oversight of peer review policies; coordinates information technology across the agency; and, coordinates the communication of health information to the public and scientific communities.

The fiscal year 2013 request will also support activities managed by the OD's operational offices. OD operations is comprised of several OD offices that provide advice to the NIH Director, policy direction and oversight to the NIH research community and administer centralized support services essential to the NIH mission.

The functions and initiatives of the OD's research offices, also known as Program, Projects and Activities, are described in detail as follows:

DIVISION OF PROGRAM COORDINATION, PLANNING, AND STRATEGIC INITIATIVES

Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) is the home for cross-cutting offices that support research in areas of emerging scientific opportunity, rising public health challenges, or knowledge gaps that deserve special emphasis. DPCPSI's scope expanded in fiscal year 2012 with the creation of a new Office of Research Infrastructure Programs (ORIP) which supports research resources that serve grantees across the NIH. In addition to ORIP, there are five offices that are described. The fiscal year 2013 budget for DPCPSI, Office of the Director and the Office of Strategic Coordination is $8,116,000.

OFFICE OF RESEARCH INFRASTRUCTURE PROGRAMS

Office of Research Infrastructure Programs (ORIP) supports research infrastructure, research-related programs, and NIH's science education efforts. Within ORIP, the Division of Comparative Medicine provides scientists with essential resources—including specialized disease-model laboratory animals, research facilities, training, and other tools—that enable research funded by all NIH ICs. The Shared and High End Instrumentation programs provide support for the purchase of research equipment, ranging in cost from $100,000 to $2,000,000. The Animal Facilities Improvement program provides funds to modernize animal facilities that support biomedical and behavioral research. ORIP also currently monitors more than 350 construction awards that have not yet reached their 20-year milestone and 147 ARRA awards for 10 years. The ORIP budget for fiscal year 2013 is $283,698,000. The Science Education Partnership Awards (SEPA) program encourages pre K–12 projects that support diversity in the research workforce as well as museum exhibits for students, teachers, and the public. In fiscal year 2013, the budget for SEPAs is $20,282,000. The Office of Science Education (OSE) develops science education programs, instructional materials, and career resources that serve our Nation's science teachers, their students, and the public. The fiscal year 2013 budget for OSE is $3,980,000.

THE OFFICE OF AIDS RESEARCH

The Office of AIDS Research (OAR) plays a unique role at NIH, establishing a plan for the AIDS research program. OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. OAR's response to the AIDS epidemic requires a unique and complex multi-Institute, multidisciplinary, global research program. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently, allowing NIH to pursue a united research front against the global AIDS epidemic. The fiscal year 2013 budget for OAR is $63,802,000.

THE OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

The Office of Behavioral and Social Sciences Research (OBSSR) was established by the Congress to stimulate behavioral and social science research at NIH and to integrate it more fully into the NIH research enterprise. To address the contribution of behavior to health and disease, OBSSR supports the activities of the NIH Basic Behavioral and Social Science Opportunity Network, a trans-NIH initiative to expand the agency's funding of basic behavioral and social sciences research. The fiscal year 2013 budget for OBSSR is $27,001,000.

THE OFFICE OF RESEARCH ON WOMEN'S HEALTH

The mission of the Office of Research on Women's Health (ORWH) is to advance NIH research on women's health. This is accomplished by catalyzing innovative research addressing the gaps in knowledge regarding diseases and conditions that affect women and in partnership with the ICs through the implementation of the NIH strategic plan for women's health and sex differences research which serves as a framework for interdisciplinary scientific approaches. ORWH promotes the recruitment, retention, reentry, and sustained advancement of women in biomedical careers and continues to lead efforts to ensure adherence to policies for the inclusion of women and minorities in NIH clinical research. The fiscal year 2013 budget for ORWH is $42,324,000.

THE OFFICE OF DISEASE PREVENTION

The mission of the Office of Disease Prevention (ODP) is to foster, coordinate, and assess research in disease prevention and health promotion at the NIH. ODP collaborates with other Federal and international organizations, academic institutions, and the private sector in formulating new research initiatives and policies to improve public health. The fiscal year 2013 budget for ODP is $6,065,000. The Office of Dietary Supplements (ODS) is within the ODP organizational structure. ODS strengthens knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public. The fiscal year 2013 budget for ODS is $27,717,000.

THE OFFICE OF STRATEGIC COORDINATION AND THE COMMON FUND

Office of Strategic Coordination (OSC) leads strategic planning for and centrally manages Common Fund (CF)-supported programs. OSC works with staff across the NIH in CF program development and implementation. The NIH CF was created by the 2006 NIH Reform Act which codified the approach of the NIH Roadmap for Medical Research to support cross-cutting, trans-NIH programs that require participation by at least two NIH ICs or would otherwise benefit from strategic planning and coordination. The CF provides limited-term funding for goal-driven, coordinated research networks to generate data, solve technological problems, and/or pilot resources and tools that will stimulate the broader research community. The fiscal year 2013 budget for the Common Fund is $544,930,000.

INTRAMURAL LOAN REPAYMENT AND SCHOLARSHIP PROGRAMS

The NIH Intramural Loan Repayment and Scholarship Programs (ILRSP) seek to recruit and retain highly qualified physicians, dentists, and other health professionals with doctoral-level degrees. These programs offer financial incentives and other benefits to attract highly qualified physicians, nurses, and scientists into careers in biomedical, behavioral, and clinical research as employees of the NIH. The Undergraduate Scholarship Programs (UGSP) offers competitive scholarships to exceptional college students from disadvantaged backgrounds that are committed to biomedical, behavioral, and social science health-related research careers at the NIH. The fiscal year 2013 budget for ILRSP is $7,393,000.

PREPARED STATEMENT OF NORA D. VOLKOW, M.D., DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH). The fiscal year 2013 NIDA budget of $1,054,001,000 includes an increase of $1,887,000 more than the comparable fiscal year 2012 level of $1,052,114,000.

The President's budget for fiscal year 2013, which has just been released, offers a timely opportunity to review NIDA's research priorities for bringing the power of science to bear on drug abuse and addiction and reducing their burden on the public's health.

A TECHNOLOGICAL REVOLUTION

The technologies of biomedical research are advancing at unprecedented rates ushering in scientific breakthroughs that are providing a deeper understanding of human genetics, chemistry, and brain circuitry. The emerging picture has the potential to transform how we prevent and treat drug abuse and addiction and its health consequences, and involves new techniques for capturing and analyzing vast and diverse datasets on everything from genetics to neuroimaging to social networks.

NIDA is poised to harness complete genome and "deep" sequencing tools and a growing portfolio of epigenetic initiatives to elucidate how biological processes and environmental factors like chronic stress and drug exposure can alter the expression of genes that influence brain organization and function and the expression (or not) of substance use disorders. For example, the recent finding in an animal model that nicotine can trigger epigenetic processes that make the brain more susceptible to the effects of cocaine could have important policy and practice implications, if it occurs also in humans.

Epigenetic research is also shedding critical new light into the mechanisms that govern the disease progression of HIV, the spread of which is closely intertwined with injection and noninjection drug-use behaviors. A cure for HIV has been elusive

because the virus is able to "hide" in a latent form in resting CD4–T cells. This allows HIV to persist for years, even with prolonged exposure to antiretroviral drugs. Understanding this "latency" effect could enable researchers to reactivate the virus and use current or future therapies to rid the body of it altogether.

The overlaying of neuroimaging data will further accelerate discovery by linking molecular and cellular data with human behavior. For example, a new functional magnetic resonance imaging (fMRI)-based approach can probe the resting brain (i.e., one not performing any specific task) to illuminate circuit-level functions that may prompt behavioral responses, including those related to diseased states or vulnerability. Individual differences found in these images could provide useful biomarkers (neural signatures) of illness risk, course, and treatment response.

The amount and diversity of data being generated by genetic, epigenetic, and imaging studies call for harmonization standards that will allow data integration across laboratories. Thus, our continuing efforts to train the next generation of addiction researchers must now take into account the urgent need for a new cadre of interdisciplinary scientists capable of developing modern analytical tools for integrating and managing large pooled data sets and for modeling and analyzing complexity.

THERAPEUTICS DEVELOPMENT

To help those already suffering from addiction, we need to expand the tools available to treat substance use disorders and their health consequences. To this end, NIDA will continue to invest in the development of addiction medications and to seek public-private partnerships with pharmaceutical companies still reluctant to play an active role due to perceived stigma and financial disincentives. Success demands both adaptable and novel approaches.

Among the "low-hanging fruit" are already-approved drugs, which NIDA is seeking to repurpose for addiction indications, saving enormous amounts of research and development time and cost. Notable in this category are: buspirone, which blocks action at the dopamine (D3) receptor (among its other effects) and may be useful in treating stimulant addiction, based on well-established findings in the animal literature; and cytisine, which acts on nicotinic receptors and has recently been shown to be about 3.5 times more effective than placebo in a smoking cessation trial.

NIDA also continues to support research to increase the effectiveness of various vaccines being tested against nicotine, cocaine, heroin, and methamphetamine. Efforts aim to increase these vaccines' immunogenicity—that is, their ability to stimulate the production of antibodies capable of blocking a drug's entry into the brain.

Finally, NIDA is actively pursuing a strategy that involves the use of medication combinations, an approach that has proven effective for treating many diseases (e.g., HIV, cancer) and one starting to show success with addiction. For example, the combination of lofexidine (a hypertension medication) and marinol (a synthetic form of marijuana's THC) has shown promise in treating withdrawal symptoms (which can trigger relapse) among marijuana-addicted individuals.

IMPROVING PUBLIC HEALTHCARE: DELIVERY AND PERFORMANCE

NIDA will harness every opportunity to translate scientific knowledge to improve strategies for combating drug abuse and addiction. This commitment includes engaging physicians as "frontline" responders and providing them with tested tools, including a Web-based screening tool that generates specific clinical recommendations. The broad availability of these resources is an important step toward integrating substance abuse screening, brief intervention, and referral to treatment (SBIRT) into routine medical care, which will enable better healthcare decisions and outcomes.

NIDA will also capitalize on the Affordable Care Act to study how innovations in service delivery, organization, and financing can improve access to and use of effective prevention and treatment interventions. Because so few people access treatment, coupled with the more than $600 billion that drug abuse and addiction cost society each year, even a marginal increase in treatment use and retention could have a sizeable public health impact—for individuals, families, and society as a whole.

To help get evidence-based treatments to providers in a variety of settings, NIDA uses collaborative research infrastructures designed to deploy proven strategies rapidly and effectively. For example, NIDA's Criminal Justice-Drug Abuse Treatment Studies (CJ–DATS) network promotes multilevel collaborations to test proven treatment models in the criminal justice system, disproportionately affected by both drug abuse and HIV. One example, called "Seek, Test, Treat, and Retain," expands access to HIV testing and treatment, ultimately reducing HIV spread.

STAYING AHEAD OF THE CURVE

NIDA continues to monitor drug abuse trends across different populations. Particularly worrisome are the trends pertaining to marijuana use, on the rise after about a decade of decline; the emergence of an ever-evolving array of synthetic drugs (e.g., spice and bath salts) that are sending users to emergency rooms nationwide; and the continued high rates of prescription drug abuse, which have resulted in a quadrupling in unintentional overdose deaths in this country since 1999. NIDA is addressing all these problems through both broad-based prevention efforts and targeted initiatives.

Prescription drug abuse is one such targeted area that demands a multifaceted approach. NIDA's long-term strategy to help reverse this trend includes:

—research to understand the factors that influence an individual's risk, treat those already addicted, and develop pain medications with reduced abuse potential;

—physician education to improve pain treatment while minimizing prescription drug abuse; and

—community engagement exemplified by NIDA's leadership of a multiagency effort to create a Surgeon General Call to Action to reduce prescription drug abuse among youth.

In closing, NIDA pledges to continue to tackle the emerging and significant public health needs related to drug abuse and addiction, taking advantage of unprecedented scientific opportunities to close the gaps in our knowledge and develop and disseminate more effective strategies to prevent and treat drug abuse and addiction.

PREPARED STATEMENT OF KENNETH R. WARREN, PH.D., ACTING DIRECTOR, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Mr. Chairman and members of the subcommittee: I am pleased to present the President's budget request for the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the National Institutes of Health (NIH). The fiscal year 2013 NIAAA budget of $457,104,000 for the NIAAA reflects a decrease of $1,868,000 less than the comparable fiscal year 2012 level of $458,972,000.

SCOPE OF THE PROBLEM

The Centers for Disease Control and Prevention (CDC) ranks alcohol as the third leading cause of preventable death in the United States, and the World Health Organization lists alcohol as one of the top 10 causes of Disability Adjusted Life Years in the United States. And, according to a new study by the CDC, the cost of excessive alcohol consumption in the United States reached $223.5 billion in 2006.

On a more personal level, I would venture that each of you knows someone who has experienced an alcohol-related problem. It could be a child who has difficulty in school as a result of prenatal alcohol exposure. Perhaps you have a relative or colleague who is one of the almost 18 million people who suffer from alcohol abuse or dependence. Alternatively, your son or daughter may be one of the more than 40 percent of college students who binge drink, many of whom experience blackouts, not remembering where they were, what they did, or with whom. You may know one of the 97,000 college students to experience alcohol-related sexual assault or heard the frustration of a college student trying to study while the alcohol-fueled party raged in the room next door. Many of us also have friends that grew up in a household where alcohol was a problem; in fact, 1 in 10 children in the United States grow up under such circumstances. Clearly, alcohol related problems are not reserved for the middle-aged, nor are they only experienced by those who drink.

RESEARCH

NIAAA supported research is advancing our understanding of alcohol-related problems across the lifespan. By translating this research into new and better prevention and treatment approaches we have the ability to enhance the well-being of individuals, their families, and society-at-large.

Much of what we have learned about alcohol use and alcohol use disorders in the U.S. population comes from analyses of NIAAA's National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Beginning in 2012, the third wave of NESARC will collect DNA samples in addition to detailed information on alcohol use, alcohol use disorders, and related physical and mental disabilities from an estimated 46,000 participants. This rich resource of genetic and other data will enable future studies comparing whole genome sequences to identify interactions between environmental and genetic risk factors that are associated with harmful alcohol use

patterns and their associated disabilities. Survey data on the distribution of alcohol-related problems and treatment utilization will inform treatment delivery systems to better help those in need of services.

Research on individuals at different stages of life and at different points in the trajectory of their alcohol use and related problems underscores the importance of early identification and intervention in reducing future health problems. This is true for:

—children exposed to alcohol in utero;
—children and adolescents using alcohol and/or at high risk for alcohol-related problems; and
—individuals who exceed the low risk drinking guidelines, including those with alcohol dependence.

One of the barriers to intervening early with children with fetal alcohol spectrum disorders is identification of affected children given the wide range of physical, behavioral, and cognitive effects that may result from prenatal alcohol exposure. Ongoing studies are demonstrating the utility of fetal ultrasound and 3D facial image analysis for earlier and improved recognition of affected children. Alcohol has also been implicated in sudden infant death syndrome and stillbirth. In collaboration with National Institute of Child Health and Human Development and NIDCD, NIAAA is supporting studies to investigate this association and the role other environmental and maternal factors may play.

Children and adolescents who drink are also vulnerable to a number of adverse outcomes. These range from immediate consequences such as academic and social problems, injuries, and death, to longer-term consequences including increased risk for alcohol dependence. Nevertheless, alcohol use increases dramatically during adolescence. Given the range and severity of consequences associated with underage drinking and the prevalence of drinking and binge drinking, routine screening and intervention for alcohol use in young people is critical. Yet many pediatricians and family practitioners cite a lack of time, a lack of familiarity with screening tools, and a lack of confidence in their alcohol management skills as barriers to screening. NIAAA designed Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide to help clinicians conduct fast, effective alcohol screens and brief interventions. The guide contains a new two-question screen and presents the first youth alcohol risk estimator chart, which combines information about a patient's age and drinking frequency to give a clinician a broad indication of the patient's chances for having alcohol-related problems. Coupled with what a clinician already knows about a patient, the risk estimator can help determine the depth and content of the clinician's response. The guide outlines different levels of intervention and presents an overview of brief motivational interviewing, an interactive, youth-friendly intervention that is considered to have the best potential effectiveness for the adolescent population. Importantly, the guide has been endorsed and promoted by the American Academy of Pediatrics.

In addition to the acute consequences of underage drinking, there is increasing evidence that alcohol use during adolescence may result in enduring functional and structural changes in the brain. Studies to date, however, cannot differentiate between anomalies which resulted from adolescent alcohol exposure and those which predated it. NIAAA is embarking on a new multi-site initiative enlisting children and young adolescents before they begin to use alcohol and following them through adolescence. These studies will use advanced neuroimaging technology as well as neuropsychological and behavioral measures to assess alcohol's effects on brain development and associated cognitive, affective, and behavioral processes. NIAAA will continue to support complementary basic animal research on the effects of adolescent alcohol exposure on subsequent brain function and behavior into adulthood. Collectively these studies will provide a more complete picture of alcohol's effects on the developing brain and potentially provide insight into the association between early alcohol use and later alcohol dependence at the molecular and structural levels.

NIAAA continues to promote screening and brief intervention for adults and encourages inclusion of it in electronic health records. The primary goal is to identify and address high-risk drinking behavior early, including advising individuals who do not meet criteria for alcohol dependence. By intervening early, providers are able to offer their patients more appealing, accessible options to address their alcohol problems, options that are less resource intensive and less expensive.

For those who continue to drink excessively, especially long term, the risk of alcoholic liver disease becomes a significant concern. In fact, 40 percent of patients with severe alcoholic hepatitis, a serious and potentially treatable form of alcoholic liver disease, die within 6 months of the onset of the clinical syndrome. NIAAA has launched a new initiative to foster close collaboration between basic scientists and

clinicians expediting the translation of emerging findings into more effective treatment strategies. Of particular interest is the connection between the gut, liver, and brain and how perturbations to one organ may aggravate the disease state in another. NIAAA is supporting the integration of research to better understand the basic biological mechanisms that underlie the disease and the individual factors that contribute to disease susceptibility in clinical studies that will test new and improved strategies. The goal is to decrease the high mortality and morbidity associated with alcoholic hepatitis.

Developing effective treatments for alcohol dependence remains a high priority for NIAAA. Preliminary studies suggest that the smoking cessation drug varenicline (Chantix) could reduce drinking in alcohol-dependent smokers. NIAAA is currently conducting a larger clinical trial with alcohol dependent smokers and nonsmokers to assess safety and determine if varenicline reduces drinking in either group.

PREPARED STATEMENT OF JACK WHITESCARVER, PH.D., DIRECTOR, OFFICE OF AIDS RESEARCH

Mr. Chairman and members of the subcommittee: I am pleased to present the fiscal year 2013 President's budget request for the trans-National Institutes of Health (NIH) AIDS research program, which is $3,074,921,000. This amount is the same as the fiscal year 2012 enacted level. It includes the total trans-NIH support for intramural and extramural research for basic, clinical, behavioral, social science, and translational research on HIV/AIDS and the wide spectrum of AIDS-associated malignancies, opportunistic infections, co-infections, and clinical complications; as well as research management support; research centers; and training.

Within the total, the Office of AIDS Research (OAR) has provided increases to high-priority prevention research in the areas of microbicides, vaccines, behavioral and social science, and treatment as prevention research, as well as to etiology and pathogenesis research that provides the essential basic science foundation not only for AIDS-related research but for other related diseases and conditions as well. In order to provide those increases, OAR has reduced and redirected funds from other areas, including natural history and epidemiology, therapeutics, and training and infrastructure support.

THE AIDS PANDEMIC

The HIV/AIDS epidemic continues to expand. UNAIDS estimates that in 2010, more than 34 million people were living with HIV/AIDS; 2.7 million were newly infected; and 1.8 million people died of AIDS-related illnesses. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that more than 1.2 million people are HIV-infected; and someone is infected with HIV every 9½ minutes. AIDS disproportionately affects racial and ethnic populations, women of color, young adults, and men who have sex with men. The number of individuals aged 50 years and older living with HIV/AIDS is increasing, due in part to antiretroviral therapy, which has made it possible for many HIV-infected persons to live longer but also due to new infections in individuals older than the age of 50. The AIDS pandemic has devastating consequences around the world in virtually every sector of society. Further research to improve prevention and treatment is urgently needed. Advances in prevention and treatment also will have extensive economic benefits.

30 YEARS OF EXTRAORDINARY NATIONAL INSTITUTES OF HEALTH AIDS RESEARCH ACCOMPLISHMENTS

HIV, the virus that causes AIDS, is one of the most complex pathogens to affect human health and challenge biomedical research. In the three decades since AIDS was first recognized, NIH has established the world's leading AIDS research program. This investment in HIV research has transformed the disease from a mysterious and uniformly fatal infection into one that can be accurately diagnosed and effectively managed with appropriate treatment. A recent study estimated that 14.4 million life-years have been gained among adults around the world since 1995 as a result of AIDS therapies developed through NIH-funded research.

NIH research has resulted in landmark advances that have led to:

—the co-discovery of HIV, the virus that causes AIDS;

—development of the first blood test for the disease, which has allowed diagnosis of infection as well as ensured the safety of the blood supply;

—the critical discovery of key targets to develop Antiretroviral Therapies (ART) and multi-drug regimens that have resulted in improved life expectancy for those with access to and who can tolerate these drugs;
—the development of treatments for many HIV-associated coinfections, comorbidities, malignancies, and clinical manifestations, with benefits for patients also suffering from those other diseases;
—groundbreaking strategies for the prevention of mother-to-child transmission, which have resulted in dramatic decreases in perinatal HIV in the United States;
—demonstration that the use of male circumcision can reduce the risk of HIV acquisition;
—the first step in proving the concept that a vaccine to prevent HIV infection is feasible; and discovery of two potent human antibodies that can stop more than 90 percent of known global HIV strains from infecting human cells in the laboratory;
—demonstration of the first proof of concept for the feasibility of a microbicide gel capable of preventing HIV transmission;
—demonstration that the use of therapy by infected individuals can dramatically reduce transmission to an uninfected partner;
—groundbreaking research regarding Pre-Exposure Prophylaxis (PrEP), examining whether the use of antiretroviral treatment regimens by some groups of high-risk uninfected individuals could reduce the risk of HIV acquisition;
—discovery that genetic variants may play a role in protecting some individuals, known as "elite controllers," who have been exposed to HIV over an extended period, from developing symptoms and enabling them to control the infection without therapy;
—critical basic science discoveries that continue to provide the foundation for novel research; and
—progress in both basic and treatment research efforts aimed at eliminating viral reservoirs in the body, which is, for the first time, leading scientists to design and conduct research aimed at a cure.

EXTRAORDINARY OPPORTUNITIES FOR FISCAL YEAR 2013

Advances made by NIH investigators have opened doors for new and exciting research opportunities to answer key scientific questions that remain in the search for strategies to prevent and treat HIV infection both in the United States and around the world, and represent the building blocks for the development of the OAR Trans-NIH AIDS research budget:

Investing in Basic Research.—OAR will increase support for basic research that will underpin further development of critically needed vaccines and microbicides.

Encouraging New Investigators and New Ideas.—OAR will provide additional support for innovative multi-disciplinary research and international collaborations to develop novel approaches and strategies to eliminate viral reservoirs that could lead toward a cure for HIV.

Accelerating Discovery Through Technology.—OAR will increase funds to support critical studies in the area of therapeutics as a method to prevent infection, including treatment to prevent HIV infection after exposure; Pre-Exposure Prophylaxis (PrEP); a potential prevention strategy known as "test and treat," to determine whether a community-wide testing program with treatment can decrease the overall rate of new HIV infections; and improved strategies to prevent mother-to-child transmission. A key priority is to evaluate prevention interventions that can be used in combination in different populations, including adolescents and older individuals.

Improving Disease Outcomes.—OAR will target funding for NIH research focused on developing better, less toxic treatments and investigating how genetic determinants, sex, gender, race, age, nutritional status, treatment during pregnancy, and other factors interact to affect treatment success or failure and/or disease progression. Studies will address the increased incidence of malignancies, cardiovascular and metabolic complications, and premature aging associated with long-term HIV disease and ART.

Advancing Translational Sciences.—OAR will ensure adequate resources for research on the feasibility, effectiveness, and sustainability required to scale-up interventions from a structured behavioral or clinical study to a broader "real world" setting.

GLOBAL IMPACT OF NATIONAL INSTITUTES OF HEALTH AIDS RESEARCH

Research to address the global pandemic is essential. AIDS research represents the largest component of the total NIH global research investment. Since the early days of the epidemic, NIH has maintained a strong international AIDS research portfolio that has grown to include projects in approximately 100 countries around the world. NIH AIDS research studies are designed so that the results are relevant for both the host nation and the United States. These research programs also enhance research infrastructure, and training of in-country scientists and healthcare providers. New collaborations have been designed to improve both medical and nursing education as a mechanism to build a cadre of global health leaders. Most of these grants and contracts are awarded to U.S.-based investigators to conduct research in collaboration with in-country scientists; some are awarded directly to investigators in international scientific or medical institutions.

BENEFITS OF AIDS RESEARCH TO OTHER DISEASES

It is essential to point out that AIDS research also pays extensive dividends in many other areas of biomedical research, including in the prevention, diagnosis and treatment of many other diseases. It deepens our understanding of immunology, virology, microbiology, molecular biology, and genetics. AIDS research is helping to unravel the mysteries surrounding so many other diseases because of the pace of discovery and because of the unique nature of HIV, i.e., the way the virus enters a cell, causes infection, affects every organ system, and unleashes a myriad of opportunistic infections, co-morbidities, cancers, and other complications. AIDS research continues to make discoveries that can be applied to other infectious, malignant, neurologic, autoimmune, and metabolic diseases, as well as complex issues of aging and dementia, AIDS treatment research has led to more effective drugs for multiple bacterial, mycobacterial, and fungal diseases and fostered significant improvements in drug design technologies. AIDS research has led to the development of new models to test treatments for other diseases in faster, more efficient and more inclusive clinical trials. Drugs developed to prevent and treat AIDS-associated opportunistic infections also now benefit patients undergoing cancer chemotherapy and patients receiving anti-transplant rejection therapy. AIDS research also has advanced understanding of the relationship between viruses and cancer. New investments in AIDS research will continue to fuel biomedical advances and breakthroughs that will have profound benefits far beyond the AIDS pandemic.

SUMMARY

Despite these advances, however, AIDS is not over, and serious challenges lie ahead. The HIV/AIDS pandemic will remain the most serious public health crisis of our time until better, more effective, and affordable prevention and treatment regimens are developed and universally available. NIH will continue to search for solutions to prevent, treat, and eventually cure AIDS.

Senator HARKIN. Thank you very much again, Dr. Collins, for a very provocative statement. I mean "provocative" in a good way, provoking thinking.

IMPACT OF SEQUESTRATION

Senator HARKIN. We'll start a round of 5-minute questions now.

First, Dr. Collins, I'd like to start by asking about the threat of sequestration.

Under the Budget Control Act of 2011, funding for virtually all Federal programs face a possible across-the-board cut in January. So we could approve our appropriations bill later this year, and then find that virtually every program will be cut in January 2013.

Now CBO has estimated, as I said in my opening statement, a 7.8-percent cut. Other observers, such as the Center on Budget and Policy Priorities, think the cuts could be even larger, 9.1 percent. But for the sake of discussion, we'll go with CBO's numbers.

Could you just give us a thumbnail sketch of what that would mean for NIH? I mentioned earlier, I think in my statement, about the number of cuts that would come because of that it was esti-

mated that the number of grants would shrink by more than 1,600 in 2014, by more than 16,000 over a decade.

Just gives us an idea of what that would mean in terms of overall NIH performance.

Dr. COLLINS. Senator, I appreciate the question. It is a very serious one.

We also heard this estimate from the CBO, that if the sequesters were to kick in on January 2013, that NIH would expect to lose 7.8 percent of the budget, about $2.4 billion. That would, of course, happen with the fiscal year already 3 months along. The estimate that has been put forward by an analysis would result in roughly 2,300 grants that we would not be able to award in fiscal year 2013 that we otherwise would've expected to.

That represents almost a quarter of our new and competing grants. That would result in success rates for applicants who come in with new applications or competing ones falling to historically low levels, and it would be devastating for many investigators who are seeking to continue programs that they have had funded in the past and are back for their competing renewal or who are starting things that are entirely new.

And I think the burden would hit particularly heavily upon first-time investigators who are seeking to get their programs up and going. And upon learning of something of this sort, what is already a considerable sense of anxiety in that cohort, who are our future, would only go up.

This would have across-the-board implications in terms of both basic and clinical science. We would, of course, attempt to try to prioritize those things that are most critical. But there's no question that such things as an influenza vaccine, which Dr. Fauci can tell you much more about, in terms of a universal vaccine, would be slowed down; that efforts in cancer research would be slowed down; that the common fund, also a component of the NIH budget where we have a lot of our venture capital space, we would not be able to start new programs, such as one focused on how to bring together cellphone technology and prevention in health, which is a very exciting new area.

All of those things would be put at great risk by this kind of outcome.

NATIONAL CANCER INSTITUTE BUDGET RESTRAINTS

Senator HARKIN. Thank you, Dr. Collins.

And, Dr. Varmus, even if we can avoid sequestration, the budget is likely to remain tight. You've been managing the NCI with small or no increase since your return.

What strategies have you found or do you plan that will allow you to continue to make progress against cancer with these tight budgets?

Dr. VARMUS. Thank you, Senator.

Well, we've done several things to try to cope with the tight budgets. I can't print money, so that would be the ideal solution. But we have been, for example, looking very carefully at grants that get lower-priority scores, to see if there are grants that meet certain high-priority topics to make sure those get funded. We've been reorganizing our clinical trials cooperative groups to be sure

they operate effectively and are answering deep scientific questions.

As you've heard in Mr. Shelby's opening statement, we have started a new program that emphasizes the bringing together of the scientific community to help define the great unanswered questions in cancer research, the so-called provocative questions, the initiative that solicited more than 750 applications to study these deeper questions and empower the scientific community to help us define what needs to be answered in the future.

We have the ability to act on our new conception of what the genetic underpinnings of cancer are through the collaborative project we undertake with the Genome Institute on the cancer genome atlas.

All of these things are helping us, but, of course, these strategies don't solve the underlying problem of having adequate resources to support science, which costs real money.

Senator HARKIN. Sure.

Well, I am about out. Senator Shelby, I want to make sure everybody gets at least one round of questions.

Senator Shelby.

OBESITY EPIDEMIC

Senator SHELBY. Thank you, Mr. Chairman.

More than one-third of U.S. adults, as everybody at the table knows, are obese. The Deep South, my area of the country, has the highest obesity rate in the country with 6 out of 7 States having an obese population higher than 30 percent.

Obesity is most prevalent in racial and ethnic minorities, low-income populations, and those who live in rural areas. Currently, there's a limited number of the most high-risk population involved in clinical trials and other NIH-funded research.

My question to you, Dr. Collins, is how can the NIH ensure the involvement of the communities most affected by obesity?

Dr. COLLINS. A very appropriate question, Senator, and one that we are quite concerned about as we look at those curves showing increasing longevity for our population. We worry that they might flatten out and actually go the wrong way, if we're not able to get control of this epidemic of obesity and diabetes.

NIH is deeply engaged in this effort, and I'm going to ask my colleague, Dr. Griffin Rodgers, who codirects the effort in obesity research across all of the NIH Institutes, to tell you something about that plan.

Senator SHELBY. Thank you, Dr. Rodgers.

Dr. RODGERS. Thank you, Senator.

NIH supports really a broad array of activities and basic translational and clinical research related to the issue of obesity. As you point out, this is really a complex problem, and a problem that one solution will clearly not be the issue.

As a result of this, the NIH engaged in a strategic planning exercise and just published, about a year ago, a strategic plan directed to obesity, aiming at prevention in local communities, the hardest affected. You mentioned the disparities in racial and ethnic groups, and physicians' offices, bringing into the fold a whole lot of people who were previously not—including urban planners and others.

We've enlisted a number of behaviorists to work on this problem, and we have some really healthy relationships both in the private sector as well as with foundations to tackle this major problem.

Senator SHELBY. How do you get people, and I'm one of them, I'm sure, to eat an apple instead of a cheeseburger?

A cheeseburger, sometimes we crave that. We might not crave the apple. But we all know the apple is much healthier for us. Is that correct?

Dr. RODGERS. You're absolutely right. And you raised an interesting point, something that people have described as "nudge."

Sometimes if you make the default value something that is healthy, you can achieve your objective. So instead of, "Would you like fries with that?" could it be "Would you like an apple with that?"

And I'm pleased to say that many in the food industry are beginning to consider these types of approaches.

INSTITUTIONAL DEVELOPMENT AWARDS ELIGIBILITY

Senator SHELBY. Institutional Development Awards (IDeA), in its entirety, my State of Alabama is a significant recipient of NIH funding, mainly due to research grants received by one institution, the University of Alabama (UAB), of course.

While their success provides significant benefits to both the State and the Nation through medical breakthroughs and economic investment, I'm concerned that its success puts other institutions in Alabama at a competitive disadvantage to similar schools in the IDeA area.

The goal there, I understand, is to broaden the geographic distribution of the NIH funding to institutions that have a historically low success rate. However, many institutions that could benefit are unable to compete for this funding, because the State they reside in is ineligible due to the success of just one institution.

The fiscal year 2012 bill included report language in support of revising current eligibility criteria. No update was provided in the congressional justification for fiscal year 2013.

Dr. Collins, my question to you, can you discuss the progress you've made in response to this language, if you have one?

Dr. COLLINS. Senator, I appreciate the question, and we are very much supportive of the IDeA program, and you've correctly cited it's an effort to try to make sure that institutions that are in States that don't have particularly heavy research investments are still able to compete for funds to be able to do good science.

As I understand it, Senator, the way in which the IDeA program is defined, in terms of which States are eligible, is not something that NIH has control over, but that in fact is something which is in the hands of the Congress.

We recognize that the IDeA program is not entirely in sync with the Experimental Program to Stimulate Competitive Research (EPSCoR) that the National Science Foundation (NSF) supports, which has a similar intention but a slightly different definition.

We are happy to continue to explore this, but we are unable to do so all on our own.

Senator SHELBY. Thank you.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Shelby.

Let's see, this will be Senator Brown.

STATEMENT OF SENATOR SHERROD BROWN

Senator BROWN. Thank you, Mr. Chairman.

Thank you all for being here and for your public service. All six of you are part of the reason that life expectancy is 30 years longer than it was a century ago, so thank you for that.

My first question is for Dr. Collins, and then a question for Dr. Fauci.

NATIONAL CHILDREN'S STUDY

The National Children's Study (NCS), what you're doing is impressive, following children from birth to age 21. In 2008, Case Western Reserve University School of Medicine in Cleveland, where Dr. Collins recently visited, was awarded two study center contracts to research children in Lorain and Cuyahoga counties, two urban, industrial counties that have a pretty diverse population and pretty widespread poverty.

Case Western Reserve University has worked with community partners, such as Battelle Memorial Institute, the Cuyahoga County Board of Health—that's Cleveland—and the Lorain County General Health District. They employed some 60 people for research and data collectors.

It's been brought to my attention that NIH found that the study's geographic approach is too expensive. It seems to back off that, and my understanding is that the seven original sites conducting this research are opposed to making that change.

It seems you're missing a whole cohort of children that are coming to the office rather than going to the community.

Can you explain to me what are your thoughts in reversing that direction, that decision?

Dr. COLLINS. Certainly, Senator, and thank you for the question.

We are very much invested in the success of the NCS as a critical way of assessing environmental and genetic risk factors for many disorders that affect individuals, with the goal then of ascertaining and following 100,000 kids from even prior to pregnancy, through the pregnancy, and on to age 21.

We've conducted over the last 3 or 4 years a series of Vanguard studies to try to assess what is the best way to ascertain such a large number of individuals. And what we've learned through that process, as well as the evolution of the way in which science is being conducted and the way in which healthcare is now possible to deliver, is that there may be ways to do this study which are actually at least as effective and considerably more efficient.

And as a result of that, and what we've learned from the Vanguard study, there is consideration underway that main study might be focused in a different way than knocking on doors, which had been the original plan.

Knocking on doors turns out to be very expensive, and it turns out also to be quite difficult to ascertain a sufficient number of cases, whereas working through providers—and again, geographically distributed providers—provides us a better opportunity to do this in a fashion which can actually save taxpayers' dollars.

But we're very sensitive to the issues you raise. This needs to be a study of children in this Nation that does not leave out those who, at the present time, don't have much in the way of health coverage.

And so the main study, which is still in the process of having its design worked out, will have some serious attention paid to that issue, so that we have a representative group of children, not necessarily ascertained in the original way, in terms of door-knocking but which does in fact give us the information we need to know about genetics, about environment in multiple different groups across socioeconomic status.

And I guess I would just encourage those who are concerned about the change to be part of the process that's going forward now, including a major meeting in the advisory group next month, to be sure that we're getting all the input we need to design a study that is going to give the answer that the Nation needs.

TUBERCULOSIS: PREVENTION, DETECTION, AND TREATMENT

Senator BROWN. Thank you.

One other question, Mr. Chairman.

Dr. Fauci, thank you for your work on infectious disease. As you know, March 24, this last Saturday, was World Tuberculosis Day, commemorating the day in 1882 when the cause of tuberculosis was discovered, as you know.

It's not much of a problem in this country. It's still a problem, obviously. It's not expensive to cure, as long as people take their medicines. You know all of that of course.

One million children will die of tuberculosis (TB) in the next 5 years around the country, as you also know, and more than 10 million children were orphaned just, I believe, last year alone because of TB.

Most alarming is the spread of multidrug-resistant (MDR) and now extensively drug-resistant TB (XDR–TB). The cures for MDR are there. The cure for XDR is significantly more difficult.

What are we doing? What is your Institute doing to foster the development of diagnostic drugs? What are we doing, especially to prevent, detect, and treat TB? And how do we manage the pockets, especially of XDR–TB, around the world and particularly in India and in sub-Saharan Africa?

Dr. FAUCI. Thank you for that question, Senator Brown.

This is truly a very important problem that has slipped off the radar screen, because of the victims of our success in the developed world, as you mentioned. But there are 1.8 million deaths with TB worldwide with an increasing percentage being MDR and XDR TB.

To your question, what we have been doing over the past several years, most intensively over the past 5 to 10 years at NIH, has been to try and bring the science of tuberculosis into the 21st century. All of the advances in molecular biology, in sequencing and drug targeting, have really not been applied as robustly as it should have been to tuberculosis.

So, we are engaging in rather intense partnerships, with industry and public-private partnerships, for the screening and development of drugs for what we call point-of-care diagnostics. One of the real tragedies about tuberculosis is we're using the same diagnostic

test that was used a century ago, namely looking into the microscope to look for, in a very insensitive way, the tubercle bacillus without even knowing just by looking at it whether it's sensitive or resistant to the common drugs.

We've now been involved in developing point-of-care diagnosis that can tell you within a couple of hours, for example, not only is it TB but is it going to be MDR TB.

We are now on the way to developing a vaccine. It's curious that we have a vaccine for TB that's been around again for a century that doesn't work on respiratory TB at all, which is the most common form of spread.

So, these are all the kinds of things that we've accelerated intensively over the last several years in both the control and, hopefully, it sounds maybe pie in the sky but people are starting to think about it now, is major control and in some countries even elimination of TB.

So we're very excited about the efforts, and we will continue to make them a high priority.

Senator BROWN. Thank you.

Thanks, Mr. Chairman.

Senator HARKIN. Senator Moran.

Senator MORAN. Chairman, thank you very much.

Doctors, welcome. One of the first visits that I made after becoming a member of the United States Senate was to the University of Kansas, where I saw research, basic research in pharmacology, pharmaceutical drugs being developed. And this research seems to me to be so beneficial.

And, particularly, I would highlight an example of collaboration between the University of Kansas, NCI, and the Leukemia and Lymphoma Society. And it seems to me, if we're going to get the best opportunities out of our investment, it is this public-private collaboration that's going to make a significant difference.

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES ROLE AND RESPONSIBILITY

And I want to talk, at least in this round of questions, about the National Center for Advancing Translational Science (NCATS).

How do we turn medical discoveries into life-saving treatments and cures? And my assumption is that's the goal of this new center. Is there a problem? Does that not occur adequately today in the absence of NCATS? So in other words, what role will NCATS play in improving the circumstance, if there is a problem to overcome?

What are the impediments toward getting that basic research and pharmacology into those drugs that save and cure and treat? And is there any incompatibility with what the private sector, what drug companies are doing, and with what NCATS is attempting to accomplish?

And then finally, perhaps this is for Dr. Varmus, but what will be the relationship between NCI and NCATS in this process?

Dr. COLLINS. Thank you, Senator Moran, for a very interesting set of questions, and one that is very much on the minds of many of us as we try to make sure the deluge of basic science discoveries that are pouring out of laboratories move as quickly as possible into their translational and clinical benefits.

You mentioned this relationship between Kansas and NCATS, and the Leukemia and Lymphoma Society.

Senator MORAN. I did it to give you a heads up as to my question, so you could anticipate it.

Dr. COLLINS. We're very excited about this particular program, because it's already now enrolling patients into a clinical trial.

I'm going to ask Dr. Insel, who is now the Acting Director of NCATS, to address some of the questions you've posed about what we aim to accomplish with this newest part of NIH.

Dr. INSEL. Thank you. It's an honor to be able to tell you a little bit about this.

I think the first thing to be clear about is that all 27 Institutes and Centers at the NIH have an investment in this kind of translation going from fundamental discoveries to making changes in health. That's what we do.

What this new entity will do, and as the chairman said before, this new entity is essentially just putting under one roof many programs that were already there.

But this is an attempt to develop the tools and to develop some new procedures that make it easier for the other 26 Institutes and Centers to succeed.

So this is a great example. This is a case in which we were interested in taking a compound that was already available in the pharmaceutical industry but not being used very much, one that was developed for rheumatoid arthritis, and developing a process by which we could screen all of the drugs that were out there, to see whether they might hit new targets that might be helpful for a disease that no one had ever considered before.

In this case, a drug for rheumatoid arthritis turned out to be very helpful for a particular form of leukemia. And then we could go to our colleagues in Kansas, who have one of the NCATS centers, the Clinical and Translational Science Awards, and get them to begin to develop this, working with the Leukemia and Lymphoma Society to have this partnership to potentially develop a new treatment for this form of leukemia.

Senator MORAN. I appreciate that story very much. It was very impressive, again, for me to see in the laboratory.

Why does that research not take place elsewhere? Why is NIH such an important component in bringing these, as you say, in this case, a drug that existed but not, I assume, thought of to be used for another purpose?

Is it the NCI that is necessary to get us to move in the directions of this new thought, these new opportunities?

Dr. INSEL. Well again, I would want to make clear that I think the NCI and many other Institutes have a stake in doing just this. The question is whether you want to do it 26 times or you want to do it once.

So in the case of developing, for instance, a procedure to move compounds from the pharmaceutical industry into academic settings, we all do that at all the Institutes to some extent. It's a bit of an impediment. It gets complicated.

There are templates that can be developed that will make that much easier doing it once instead of doing it multiple times. And there are tools that we need.

In this case, this was a particular repository that was developed by the folks at NCATS that collected in one place all the medications that were out there, so we could do a single screen instead of having to break it up into many different attempts.

So NCATS is really an enabler, essentially. We sometimes call it a catalyst for innovation. It's a way of putting under one roof many of the tools that all of us need to get things done faster.

Senator MORAN. Thank you very much, Doctor. Thank you.

Dr. Varmus.

Dr. VARMUS. Well, let me just add one or two words here.

As you pointed out, Senator, the categorical institutes have a deep investment in translational research activities, and the NCI is no exception to that, with well more than $1 billion a year being invested in these topics.

In the case of chronic lymphocytic leukemia, we have a major program to look at the basic genetics. It's a disease that is a smoldering disease which becomes acute, and we have very few treatments when the disease enters its acute phase.

The intramural program of the NCI came to the chemical genome screening center to help find drugs that might be repurposed, drugs that the company might have little interest in, because it's off-patent, and we were fortunate to have this drug turn up.

Now this trial we see as emblematic of what NCI might be involved in, in working with NCATS. In this case, as you've heard, the trial is being sponsored by the Leukemia and Lymphoma Society. But I think this is a good example of how the interaction between the NCATS and individual institutes like ours might be very beneficial.

Senator MORAN. Thank you all very much.

Senator HARKIN. Thank you, Senator Moran.

Senator Pryor.

Senator PRYOR. Thank you, Mr. Chairman and Ranking Member. Thank you for holding this hearing today, and I want to thank the panel for being here.

I'm going to focus my questions with Dr. Collins and Dr. Varmus.

I'm a cancer survivor. I survived clear-cell sarcoma about 15 years ago. Thank you for all your work and all you do in the cancer area, and every other area, for that matter.

PANCREATIC CANCER

I want to ask about pancreatic cancer. As I understand it, it's the most lethal of the common cancers. It's the fourth-leading cause of cancer death. This year, more than 43,000 Americans will be diagnosed with pancreatic cancer, most of whom will die within 1 year of their diagnosis, because the disease is usually too far advanced by the time it's discovered.

And I know in this subcommittee, we're careful to avoid trying to tie the hands of scientists by directing too precisely the appropriated money, on how it should be spent. But I'm troubled that while survival rates of many cancers are steadily improving, one of the most lethal forms of cancer, pancreatic cancer, remains at about 6 percent.

And I look at the model for breast cancer. I'm not sure that's the best model, but I do look at that model and some of the focus there.

I'm wondering if NIH would consider using that breast-cancer model to try to go after pancreatic cancer.

Dr. VARMUS. Thank you for that, Senator.

As someone who has lost several friends to this disease over the last decade and who has worked in my own laboratory on this disease, I appreciate the devastation the disease causes and the difficulty of trying to make headway against it.

Indeed, of the cancers that we work on, I'd say progress has been relatively small in the clinical arena, as you point out.

But there is a great deal of reason for optimism in this domain.

First of all, we have a much larger number of investigators working on the disease, and we have some scientific opportunities that are very dramatic that I'd like to outline for you very briefly. As a result of both factors over the course of the last decade, the amount of money that the NCI spends on this disease, despite the flattening of our budget, has gone up 300 percent.

The model that you alluded to of breast cancer is useful, because one of the things that's been a factor in increasing our attention and increasing our spending on this disease has been the role of advocacy groups, such as the Lustgarten Foundation and several others, that have helped to incentivize NCI-supported investigators to work on this very difficult problem.

There's been a number of dramatic changes in our view of this disease in the last few years, one as a result of being able to take DNA from tumors and examine the underlying damage in the genomes of those cells, to try to understand the disease more profoundly.

One of the consequences of that analysis has been to perceive that pancreatic cancer does not arise in a matter of months. It rises over the course of one or two decades. And that's an important fact, because we know now that there is quite a large window of opportunity for detecting the disease earlier than we have seen heretofore. And that's, of course, a major factor in this disease, the symptoms appear very late when the disease has often spread. And unlike certain other cancers that manifest themselves on the skin or with symptoms at an early stage, it's been difficult to diagnose this disease at an early phase.

Second, we've been able to understand the relationship between the tumor itself and the cells that surround it that make the disease somewhat impermeable to some of the therapies that have been used for other cancers. And there are new ways to try to make the surrounding material more permeable to cancers.

Furthermore, there's been a number of mouse models of the disease that were previously difficult to create that are now being used to try to understand the physiology of the disease and to test treatments in animal models.

All those things give me considerable optimism for the future.

PRIORITIZING CANCER FUNDING

Senator PRYOR. Well, does that mean, though, that you're going to prioritize it in terms of funding and try to invest more there?

Dr. VARMUS. It is prioritized, Senator. And I mentioned earlier that, in this period of budgetary constraint, the NCI has been paying special attention to grants that might in the past have been un-

funded because they fell below what we used to call a pay line. And now we examine quite a number of grants that get priority scores that are perhaps less high and look at them for the diseases that fall in certain categories where we made less progress in therapeutics, neuroblastoma, lung cancer, pancreatic cancer, ovarian cancer, and others. And we frequently fund grants that scores may have been a little less than others but nevertheless represent high-priority areas for us.

Senator PRYOR. Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Pryor.

Senator Cochran.

INSTITUTIONAL DEVELOPMENT AWARD PROGRAM FUNDING

Senator COCHRAN. Mr. Chairman, thank you very much.

Let me ask about a program that is designed to help ensure a broader base of financial support to research institutions and those who are in university settings, and who are engaged in research that has unique applications and importance to the medical community and the life of the citizens of our country.

This is done through a program called the Institutional Development Award (IDeA), and the whole point is to broaden the geographic distribution of NIH funding in biomedical and behavioral research programs.

In my State, we have seen some very important strides made in these programs. There are 23 other States in the same boat as my State of Mississippi.

The bill that we have provided funding in directed that certain areas be undertaken for research and review. The Centers of Biomedical Research Excellence (COBRE), which is a Competitive Grant Program, received an increase of $45.9 million through this program. But NIH said that they're not going to be able to use the funds, and so this year's bill reduces funding by about $50 million.

I'm asking, what do we need to do, use different wording, put a star by the provision in the bill that these are funds that are intended to be used and for the purposes that the Congress stated? Who wants to take that on and explain what's going on to me?

Dr. COLLINS. Senator, I appreciate that question and clearly the IDeA program is one that NIH is proud of. And before you came in, Senator Shelby was asking whether Alabama could be added to the club, because, clearly, the 23 States that are eligible for this program depend on the opportunity to be able to compete for NIH dollars, and lots of good science gets done as a result.

I want to reassure you that the dollars that were allocated to the IDeA program in fiscal year 2012, the year that we're currently in, are going to be utilized and are going to be utilized, I think, quite effectively. We are going to follow the Congress's instructions here in terms of how to make the most of this additional allocate of almost $50 million, which for the IDeA programs represents a 22-percent increase in that program in fiscal year 2012 compared to fiscal year 2011.

So, we will be funding both COBRE program that you referred to. Also, as we were asked to do, the new Center for Clinical and Translational Science is part of the IDeA program, and that process is already very much underway, and we will make sure that

we do everything you would want us to, in terms of reviewing and choosing the very most competitive programs to award those dollars to.

Going forward in fiscal year 2013, you will notice that the dollars do not stay at that same level. We are certainly very enthusiastic about IDeA, but at the same time, we have so many pressures on so many other parts of the program that the President's budget reflects that, in terms of decisions that were made in putting together that fiscal year 2013 budget.

But again, I do want to reassure you, as far as fiscal year 2012, we are going to spend those dollars in a very, I think, aggressively innovative way and to the benefit of the IDeA States.

Senator COCHRAN. Thank you very much.

And thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Cochran.

I just might add on that IDeA program, I was not one of those States either. But I'm not clamoring for Iowa to be one, because while I understand the interest of States to find funding for a lot of different things, I think Senator Shelby said it in his opening statement: We want the best science rewarded.

If it's not in Iowa, then it's someplace else. But it's got to be the best science.

We're not in the business of just spreading money around. We're in the business of trying to take the limited budget that we have and reward the best science that's out there. And we count of all of you and your advisory boards and others to tell us what that best science is. I just want to make that statement.

Senator COCHRAN. Could I have the opportunity of asking the witness whether they think this is wisely invested money or not? I think the suggestion of the question that the chairman has asked suggests that they may be funding in this program just because a Senator on this subcommittee, vice chairman of the full committee, asked for it.

Senator HARKIN. No, I just want to——

Senator COCHRAN. That's not the purpose of the question. The question was on the merits of the program, if it was justified and if the funding level and the language and all was consistent with what the department and the witnesses here thought would be an appropriate investment.

H5N1 RESEARCH

Senator HARKIN. Well, I sure hope so. I hope that is what they will do.

Dr. Fauci, over the past few months, there has been quite a controversy regarding NIH-funded researched related to H5N1 flu virus. You remember, you've been here before in the past on this?

Dr. FAUCI. Yes.

Senator HARKIN. A great flare up a few years ago from Southeast Asia, concerned about what was going to happen when it got here.

Fortunately, we found out that it wasn't very transmissible to humans. But recent research has shown that it's possible to genetically alter the virus so that it could spread from human to human.

In December, the National Science Advisory Board on Biosecurity said that this research was a "grave concern to public health." It

asked two journals, Nature and Science, to withhold some parts of the research results to reduce the risk that bioterrorists and others could misuse this information.

On the other side, however, many leading flu researchers disagree and believe the full results should be published.

As of now, a final decision on publication is still pending. There's also a voluntary moratorium among flu experts on some of the research.

You have said that you support this research. I want to know why, and what did NIH hope to learn? Is it worth the danger that a lab-made virus could be released into the world, either intentionally or by accident? And do you think the full results of this research should be published?

Dr. FAUCI. Okay. Thank you for that question, Mr. Chairman.

First of all, the issue of H5N1 and why we do the research, there is no question that influenza, in general, the potential for pandemic influenza and, in this case, specifically, the H5N1, is a clear and present danger because we still have smoldering infections with major outbreaks in chickenpox and, occasionally, a jump from a chicken species to the human species.

As you said correctly, this is not easily transmissible from human to human, and certainly not transmissible easily from chicken to human. The problem is that, as you look in the wild, you see that viruses, as they always do, evolve. And the critical question that really spurs this research is what are those factors that go into the evolution of a virus to what we call "species adapt." In this case, adapt to the human in a way that would make it transmissible. This is an absolutely, unequivocal, critically important question to ask.

So in that case, the research is really very important. We have a major program for decades that studies what we call transmissibility in species adaptability that has made us much better prepared from year to year and on the rare occasion where you get a pandemic to be able to predict and be prepared for, to respond to a pandemic. That's issue number one.

The papers in question, we're doing something that is an important approach toward understanding this phenomenon that is a real and present danger in the wild. And what they did is that they tried to characterize exactly how a virus would look if it did develop the capability of, in this case, mammal.

You use the words human transmissibility. I want to underscore that this was transmissibility from ferret-to-ferret, which is a good but imperfect model for human influenza. So there is a misperception there that this is now transmissible in human.

There was also a misperception in the information that was given out to the public that when you made a virus transmissible from a ferret to a ferret by aerosol transmission, which is the way humans transmit virus from one to another, that actually those ferrets died with high degree of mortality. And that turns out to be not the case.

So where we are now, today, is that we had a determination. We are very careful about the balance between the scientific need to know for the public health good and safety and security. We take that very, very seriously.

When it became clear that this could be what we dual-use research of concern that could possibly be used for nefarious purposes, we put it before an advisory committee that made the recommendation on the basis of the information that they had that the research was important to perform, but that perhaps parts of it, the details, might not be readily available to everyone.

WHO called a meeting, and when they looked at the data and some additional data, and some clarification, they came to a conclusion that was a little bit different. They said, in the big picture of things, the real and present danger of this happening in the wild really outweighs the possible risks of there being bioterrorists.

So, we have a disparity now of recommendations.

Tomorrow, the NIH/HHS is reconvening the National Science Advisory Board for Biosecurity, which is a nongovernment, outside group that would advise the Government, and we are the ones that originally said that we should hold back.

So we're looking forward to tomorrow and Friday when this group will reconvene and look at additional data, because there has been considerably more information that has been gathered since the original determination to hold back some of the data.

Senator HARKIN. Well, I'll look forward to that, too. In the next couple of days?

Link for Recommendations follows: http://oba.od.nih.gov/oba/biosecurity/PDF/03302012__NSABB __Recommendations.pdf.

Dr. FAUCI. Yes, Sir.

Senator HARKIN. That's very timely.

I have a follow-up on that, on H5N1, in my next round, but my time is up.

Senator Shelby.

DOWN SYNDROME

Senator SHELBY. In the area Down syndrome, Dr. Collins, I support the goal of the NCATS to invest in research that moves a potential therapy from development to market as you do. As you continue to develop aspects of the new center, this may be an opportunity to focus on conditions where comorbidities are so pervasive that research will help both the population in question and those suffering from such comorbidities.

For example, 50 percent of those born with Down syndrome, also are born with a congenital heart defect, and more than 50 percent of those with Down syndrome will suffer from the early onset of Alzheimer's disease. Yet it's extremely rare for a person with Down syndrome to suffer from a solid tumor cancer, heart attack, or stroke.

Can you discuss how NCATS will focus on diseases, such as Down syndrome, whose research could benefit many in populations?

Dr. COLLINS. Thank you for the question, Senator. I'm trained as a medical geneticist, and so Down syndrome is certainly one of the conditions that, in my clinical years, I spent a lot of time wrestling with, in terms of trying to give the best advice to children and their parents about this disorder.

As you know, this is caused by an extra copy of an entire chromosome, chromosome 21, which means that genes that are nor-

mally present in two copies are present in three. Even though it's one of the smaller chromosomes, there's still a lot of genes on that chromosome.

And it's been a big question for research to figure out which of those are the ones that are so dose-sensitive, because most of the time, if you have 50 percent more of something, it's not going to cause a lot of trouble. But, apparently, on that chromosome are some genes that do have that potential.

It's the National Institute of Child Health and Human Development (NICHD), whose Director, Dr. Alan Guttmacher, is here, who has the lead in Down syndrome research. They have put together a research protocol and a plan over the course of the last few years, and now formed a consortium bringing together NIH and other organizations to be sure we are looking at what the opportunities and gaps are.

There is some exciting research going on in terms of the mouse model of Down syndrome and even some therapeutic interventions using neuropeptides that seem to show promise in that mouse model.

In terms of the role of NCATS, again, as you heard from Dr. Insel, NCATS does not have as its goal to focus on specific disorders. That's the role of the other 26 Institutes.

NCATS aims to provide resources and to attack those bottlenecks that are slowing down everybody, and to try to see whether we could do better in terms of, when you have an idea about a therapeutic, how do you get it to the point of a clinical approval in less than 14 years and with a failure rate that's less than 99 percent? That's really what NCATS is all about.

So, NCATS should be an important addition to the landscape. But again, I think the lead efforts in Down syndrome will continue to be at NICHD.

INTERAGENCY COLLABORATIONS AND CYSTIC FIBROSIS

Senator SHELBY. Thank you.

Dr. Collins, this is a very important time, as you said, in the history of drug development. We continue to see the benefits from mapping the human genome when specific treatments for genetic diseases are being developed to target smaller and smaller populations.

This aspect of personalized medicine holds promise to treat or to cure rare diseases that plague millions of Americans.

In January, the Food and Drug Administration (FDA) approved a groundbreaking new drug for cystic fibrosis. This drug treats the underlying genetic cause of cystic fibrosis in the 1,200 people who are affected by a particular genetic mutation. This breakthrough treatment has led to tremendous health gains for those who take the drug, and may lead to the development of an innovative new class of drugs for a much larger portion of the cystic fibrosis population.

Collaboration between the NIH and the FDA has the potential, I believe, to move genetic breakthroughs more quickly through the development process and into the hands of patients by ensuring that the FDA has the tools it needs to review and to regulate the genetic treatment.

What are your thoughts on this?

Dr. COLLINS. Well, Senator, I think what you've pointed to is a really exciting development for cystic fibrosis but also a very important point you're making about the need for close collaboration between NIH and FDA, the private sector, and advocacy organizations, such as the Cystic Fibrosis Foundation, who played a big role in this recent advance in cystic fibrosis.

And if you'll permit me, I will tell you what a personal delight it was, having been part of the team that discovered that gene in 1989, to see at this point the use of that information coming forward with the drug Kalydeco.

Senator SHELBY. What can that mean to the people with cystic fibrosis?

Dr. COLLINS. So for the roughly 1,300 individuals in the country who have this specific mutation in the cystic fibrosis gene called G551D, which is unfortunately only about 4 percent of cystic fibrosis sufferers, this drug causes that defective protein to rev itself up. And the clinical results, as published in the New England Journal last year, are truly dramatic in terms of improvement in lung function, gain in weight, because cystic fibrosis is often associated with weight loss. And also, you can see the biomarker for cystic fibrosis, the sweat chloride, returning to normal in kids who are taking this drug.

Again, this special this evening that NOVA is putting on will give you a couple of examples of how that has played out.

So that is really gratifying. But you're right. We need to be sure that we can replicate that many times over.

Dr. Margaret A. Hamburg, the Commissioner of the FDA, and I have formed a joint leadership council between our senior leaders, and many of the NIH representatives who are sitting here at the table are on that council. She has also brought her Center Directors into that same place.

We have resolved together to identify the areas that are most in need of this kind of collaboration and are working quite intensively to try to do that.

Senator HARKIN. Thank you very much, Senator Shelby.

Senator Mikulski.

Senator MIKULSKI. Good morning, everybody. I'm so sorry I couldn't be here for all of your testimony. I was at the DOD on military medicine, and of course, as you know, a lot of that is right across the street from NIH, and we won't talk about the traffic jam.

Senator HARKIN. But thank you for helping with that, too.

NATIONAL INSTITUTES OF HEALTH PRIORITIES

Senator MIKULSKI. And I was effusive with Senator Inouye.

But, Dr. Collins, and to all of you, I've known you for so many years, and I just want to welcome you and let you know how glad I am to see you and how much you are appreciated. We ask you to do a lot. We hope that we have the adequate resources, and at the same time, we are deeply troubled that, as Federal employees are under attack, they seem to forget that you are the Federal employees we need and we turn to in the national interest.

I'll come back to that, because I wonder how all of that harassment, hazing, the cute one-liners in town hall meetings against Federal employees are affecting morale, recruitment, and retention, because, I think, from what I hear, standing in a bagel line or something, or a broccoli line, in Rockville, that I hear it.

But let me get right to my question. Many of you we have turned to at a time of national emergency, and I think of Dr. Fauci, when an obscure virus was beginning to kill young men in our community and escalated in our country and even into a global crisis, AIDS; when we had the anthrax scare here, et cetera.

We came together, and we really moved on a national agenda, and this then goes to, picking up on Senator Shelby, the acceleration of drugs.

Now, Dr. Varmus, you and I have talked about these things. We don't want industrial policy visits at NIH. We don't want to pick winners and losers, et cetera.

But we have compelling needs. We have the orphan drug, you know, the rare disease constellation and then we have those areas that relate to chronic illness or the impending or arriving epidemic of Alzheimer's.

And my question to you is looking at both your Center for Translational Medicine and so on, how can we look at what are compelling national needs, those that we know will impact significant parts of our population, use a significant amount of our cost for the treatment of these, some so long range, like Alzheimer's, some immediate, like diabetes, Dr. Rodgers?

One, do you think it is a valid thing to do? How can we work with you to do that? What are the right resources? And how do we avoid the industrial policy syndrome, which we certainly don't want to get into, because you do need lots of latitude for discovery.

Dr. COLLINS. Well, thank you, Senator, and by the way, congratulations to the Senator from NIH on this recent milestone of recently being recognized as the longest-serving woman in Congress. We were all cheering for that.

Senator MIKULSKI. Thank you. It was moving from the bagel line to the broccoli line.

Dr. COLLINS. Your question is a very important one. How do we in fact decide how to set priorities is what I think you're asking, and of course that's not only——

Senator MIKULSKI. And also how to accelerate?

Dr. COLLINS. And how do we speed up the process of going from basic science to therapeutics?

Maybe just as an example, because it is timely, I would mention what you just mentioned, the situation with Alzheimer's disease. So talk about a public health circumstance of enormous concern. Here we have a diagram showing the prevalence of Alzheimer's disease currently at 5.1 million, expected to rise almost to 12 million over the course of the next few years, if nothing is done about it, and with the cost going through the roof. So here is an area of potential, very serious significance.

And also, I'm happy to say, a situation where the science of Alzheimer's disease has come across quite quickly in just the last year or two, putting us in a position to be able to push that therapeutic agenda harder. And yet for many companies, diseases affecting the

CNS are not seen at the present time as being particularly commercially attractive.

Senator MIKULSKI. Do you want to say what CNS means?

Dr. COLLINS. CNS, central nervous system. I'm sorry. Brain diseases.

I'm going to ask Dr. Hodes, who is the head of the National Institute of Aging, to just say a word about the science that propels us to be particularly excited about Alzheimer's, again as an example of the exhortation you're providing us about what we need to pay attention to.

Dr. HODES. Thank you. I'd be happy to do so.

As we've seen emphasized, the byproduct of the extended longevity in the American and world population has really been the increased threat posed by diseases of late life, and Alzheimer's is certainly prominent among them.

So there's no question, as there has been for a number of years, about the public health importance and imperative. As Dr. Collins notes, what is most exciting to us all is the advance in science that really creates an opportunity, justification for optimism, that didn't exist before.

Earlier, Dr. Collins presented an example of a drug through repurposing, in this case Bexarotene, a drug that had been used to treat a kind of skin cancer, which when tested for its effect on some of the underlying processes of Alzheimer's disease in a mouse model showed absolutely dramatic effects.

Another kind of advance that has been featured, just in the past few months, has been the use of induced pluripotent stem cells and particularly the translation from a skin fibroblast from an individual with or without Alzheimer's disease into neuronal cells in a tissue culture dish, which reflect many of the underlying biochemical abnormalities of Alzheimer's disease.

The potential here for screening now in cells and tissue culture tens, hundreds, thousands of compounds, to see whether they will have an effect that provides a suggestion of which might ultimately be translated, is just one of the many examples that we are poised to capitalize upon at this time.

Senator MIKULSKI. Dr. Hodes, if I could jump in?

This is so exciting to hear. But I held a hearing 3 years ago on the issues of Alzheimer's, with my colleague Senator Bond, who was tremendously interested in this as well as arthritis. And we heard then, 3 years ago, well, we are on the brink of big breakthroughs.

So I had a legislative framework to take a look at that. I was stymied in this institution, okay? I was stymied in this institution on taking a look at this. And I won't go through my legislation. This is not about me. It's about people, which is why we're all in this.

And my question is, 3 years later, I've given up on legislation. I mean, I'm going to move my legislation. Maybe it'll happen; maybe it won't.

But I'm asking, administratively, and through the executive branch, where we have a body of knowledge and a variety of studies that are breakthrough possibilities that meet compelling human need and big budget busters, how can we move these through this process and get them into the hands of clinicians?

I've now heard about promising science, and I'm going to continue to support it, but the promise of science needs to have deliverables.

Dr. HODES. If I may, Mr. Chairman? I know we're over time.

Senator MIKULSKI. Do you mind, Mr. Chairman?

Senator HARKIN. We're over time, but go ahead and respond, please.

Dr. HODES. So with regard to Alzheimer's, recognizing the exceptional scientific opportunity and public health need, in the fiscal year 2013 budget, the President's budget proposes an additional $80 million for Alzheimer's disease research, over and above the regular NIH appropriation, as a recognition of that exceptional opportunity.

But I think your question is broader than that.

Senator MIKULSKI. It's much broader.

Dr. HODES. And that is how do we, at a time where resources are in fact constrained, make decisions about how to set the priorities to the way that benefits the public in the greatest way? That is our toughest challenge. That's what we sit around the table with the Institute Directors on Thursdays and try to wrestle it. That's what all 27 of the Institute and Center Directors are charged with, in terms of surveying the landscape, trying to see where the gaps are. What we don't want to do is be overly top down.

Senator MIKULSKI. You haven't answered my question.

Dr. HODES. I thought I was getting there, but maybe I——

Senator MIKULSKI. I feel the pressures of time, Doctor. And I don't mean to be interruptive or whatever. But I know you're working hard on it. But do you have an answer to my question?

And if not, it's not a hostile or aggressive question. I just feel the demands of time on our population, the frustrations that families and patients have. You meet with advocacy groups. You're well-known for your accessibility.

Do you have an answer on how we can do this without industrial policy?

Dr. HODES. Senator, I share your frustration and your passion, believe me. The reason I went into research was because of the concerns that we weren't going fast enough in finding answers for people who need them desperately.

I think what NIH is trying to do, in answer to your question, is to be sure we are looking at every possible means of promoting science rapidly. We are trying to figure out how to work with the private sector in circumstances where we can do things together.

But for circumstances where clearly things are hung up, like the bottlenecks we're now trying to tackle with this new NCATS, we are jumping out there in a fairly aggressive way, in fact, in a way that some have said was too aggressive.

But we accept that concern, because of our impatience, just like yours, to take this science that's happening right now and turn it into treatments and cures for those millions of people who are waiting for those hopes to come true.

Senator MIKULSKI. I know my time is up. Well, I want to thank you for your science. I want to thank you for your dedication and for your compassion and your humanitarianism.

Senator HARKIN. Thank you.

NEW INVESTIGATORS

Senator Moran.

Senator MORAN. Mr. Chairman, thank you. Doctors, let me just join, perhaps, the Senator from Maryland, and I was thinking about the—I think most of us spend our lives trying to create hope for other people. I hope that you take great satisfaction in the noble calling that you're pursuing in your lives and know that you are providing hope. In my view, it's the mission of the NIH to provide hope for Americans and really for people around the world that we find cures and treatments.

And so I commend you for choosing a profession, a career, a path, that I think matters so much in changing the world.

Somewhat in that regard, obviously bringing new talent and professionalism, scientists, researchers, and medical practitioners to the arena to provide that hope, I've said numerous times that one of the problems with reduced funding at NIH, or flat-funding that results in less actual money available for research, one of the reasons that that's so troublesome to me is that we're sending a message to the next generation, the potential researchers, scientists, physicians, that the certainty of their career path or the value of what they do is not recognized.

And while I say that, I don't have any basis other than perhaps common sense to say that that would be the case, and I would be interested in knowing if you can, either anecdotally or scientifically, tell me that that's a valid point to make to the American taxpayer, the merit of making certain that funding continues in a stable manner.

And one perhaps less philosophical question, I would like to hear, Dr. Insel, if there is a—this is a question that comes to me just knowing of your center. What's going on that will be helpful to our returning veterans related to mental health? And is there a relationship between what you do and the Department of Veterans Affairs (VA)?

Dr. COLLINS. I'll take the first part of your question, and then ask Dr. Insel to jump right in.

Certainly, for a new investigator who has recently gone through extensive research training and is now starting up their own independent research program in one of our Nation's great universities or institutes, this is a somewhat scary time. They can see what's happened in terms of the likelihood of being funded if you send your best ideas to NIH, which traditionally during the last 40 years has been in the range of 25 to 35 percent, and which last year, the last year we have full numbers for, fell to 17 percent.

That means that an awful lot of that effort comes away without support. And, therefore, those investigators spend even more of their time writing, revising, resubmitting, hoping that they will actually make that cut and be able to get started.

And certainly, if I had to pick one thing that I would say would be most healthy for the American biomedical research future, it would be stability. The feast or famine just doesn't work in this circumstance. You want to give investigators the confidence that if they have good ideas, and if they work hard, and if they produce publications that change the direction of a particular field, they

make insights, they make breakthroughs, they take risks, that there is a career there. And it's difficult when things are bouncing around, as they currently are, for particularly early stage investigators to have the confidence that there's a pathway for them.

That trickles down, and others who are sort of earlier in their decisionmaking hear about it and begin to wonder whether this is a career that they want to invest themselves in.

That's not happening in other countries, but that's happening, certainly, in the United States.

RECRUITMENT OF SCIENTISTS

Senator MORAN. Is there an opportunity for that talent that we're trying to retain in the United States? Is there a movement abroad? Would research scientists in the United States conduct their research elsewhere or pursue—are we competing, I guess is the word, in a global economy, for the best talent?

Dr. COLLINS. We are, and, of course, we have greatly benefited over the years in being able to recruit talent from other countries, and we continue to.

In many instances, those individuals would come and be trained in our country and then would stay and become part of this remarkable innovative community.

It is less likely now that those individuals will stay. It's easier, in many ways, to go back to their countries, where there's more support now plus perhaps they see the environment here as not as friendly.

So, yes, that dynamics have certainly changed.

POST-TRAUMATIC STRESS DISORDER

Dr. INSEL. So very quickly, with my day job hat on, from NIMH, we're particularly concerned about the needs of returning veterans. Estimates are somewhere north of 300,000 who will develop post-traumatic stress disorder (PTSD) or a related disorder that will require some kind of care in the community or potentially through the VA.

We work closely with the VA, but our largest single project currently is actually with the DOD, working with the Pentagon on a massive project now with more than 30,000 soldiers involved, to look at soldiers, with active-duty soldiers, and following them through their service to figure out what we can do to make sure that they don't develop PTSD, traumatic brain injury, or other problems.

That was really generated by the increase in suicide that was reported by the Army, and we've been charged with trying to turn those numbers around.

Senator HARKIN. Thank you, Senator Moran.

Dr. Fauci, I said I have a follow up on H5N1, and that's not true. I have a follow-up question but not necessarily on H5N1, except to say I just wonder if we've been kind of lulled into a state of complacency on this. And we know viruses mutate all the time. If this does mutate into a form that is transmissible, it could be devastating.

Dr. FAUCI. Right.

Senator HARKIN. And hopefully, we're prepared for that.

Dr. FAUCI. Right.

IMMUNOTHERAPY ADVANCEMENTS

Senator HARKIN. But what I want to ask you about was a question that you've responded to previously before this subcommittee and it has to do with food allergies. We talked about this a lot in the past.

I've been told that small trials involving immunotherapy have been very encouraging in treating children who have peanut, egg, and/or milk allergies. As I understand what happens, these kids are given small amounts, and then larger and larger amounts.

Again, I guess for some children with very severe cases, this isn't enough, so they're given both that plus a drug.

From what I understand, what's needed now are phase II trials for these treatments, as well as studies that could explain how they're working.

So, again, what's happening in this area? Why does immunotherapy work for some and not for others? And how are you proceeding with the phase II trials?

Dr. FAUCI. Okay. Thank you for that question.

We have, as I've told you and this subcommittee before, over the last several years, dramatically increased the resources that we have put in on food allergy. Having said that, we started off at a low number. So at a time when the NIH budget has been flat, we have been progressively increasing by a considerable number of factors.

We still are not where we want to be, but within that realm, answer to one of your specific questions, it is unclear at present why some people respond to this early desensitization by giving small amounts of what would ultimately be desensitizing antigen—in this case, it would be peanut or chocolate or something like that.

Phase II trials are, as you know, the next stage after you show that a particular intervention is safe in a phase I to go in and get more information from a phase II. We are very much right now involved in making that next step to go to phase II trials and some of those interventions. But it is not in a situation where we are having a large enough trial to definitively answer the questions, but that is the next stage that we're going.

So we're right at the point and we are working with a number of the societies. In fact, I just met less than 2 weeks ago with our food allergy constituency groups to discuss how we might continue in an arena of constrained resources to push this agenda, particularly in the arena of clinical trials.

Senator HARKIN. If you don't have the figure now, maybe you could just transmit it to us later on, just how much is this going to cost.

Dr. FAUCI. Right. Okay. I don't have the exact number now, but clinical trials in general, particularly when you get to phase II and phase IIB, which involves several hundreds of people, it costs a considerable amount of money.

And that's really been one of the constraints that we have, because the total budget for food allergy, although it's accelerated greatly over the last few years, is still, relatively speaking, when

you compare it to other things, rather small, which we're trying to do something about.

ALZHEIMER'S RESEARCH

Senator HARKIN. Thank you, Dr. Fauci.

I still have a minute and a half. I want to get Dr. Hodes into this area of Alzheimer's research. The President, as Dr. Collins has said a couple of times in his opening statement, again, has proposed $80 million for NIH research specific on Alzheimer's.

And where he's getting the money? He's taking it from the Prevention and Public Health Fund (PPHF), Senator, that we put into the Affordable Care Act.

I just, again, in a friendly atmosphere, want you to know that that won't happen. That is not going to happen. I will make absolutely certain that not one more nickel is taken out of the PPHF for anything outside than what it was intended for. Just as I will not go after NIH to get money for the PPHF, we're not going to take money out of that fund and put it into NIH.

Now, again, if you're wondering why I'm so upset about this, it's because this President put in his budget to take $4.5 billion out of that fund. And the Congress, in extending the unemployment insurance to the end of the year and that tax cut on Social Security, while they pay for it, they took the money out of the PPHF.

So I'm very upset about that. I'm very upset with the President and his people at the Office of Management and Budget (OMB) for what they did on that, and then to come and say, now we're going to take another $80 million. I know that sounds like a small amount but, still, after you've taken $5 billion out, and now they're just going to start nickel and diming us?

So, I just want you to know, I'm a strong supporter of Alzheimer's research, but this $80 million isn't happening. NIH has the flexibility to direct a larger share of its funding to Alzheimer's research within its own budget, assuming two things. One, there are enough scientific opportunities to warrant an increase, and, second, researchers submit enough high-quality applications.

So, again, I know all of the data and statistics on what's happening on Alzheimer's in the future. It's something we have to pay more attention to. We need more research into that area. How much more, I don't know. That's up to you. You're the experts in this area.

But this subcommittee will be more than supportive of efforts by the NIH to focus more on this, given those two conditions that I mentioned, into Alzheimer's research.

And I don't know if you have a response to that, Dr. Hodes or not, I'm not asking for a response. I just want you to know what's happening here.

Senator Shelby.

NATIONAL INSTITUTES OF HEALTH MERITOCRACY MODEL

Senator SHELBY. Thank you, Senator Harkin.

The NIH has a highly competitive, two-tiered, independent peer-review process that ensures support of the most promising science and the most productive scientists. The fiscal year 2013 budget pro-

poses to alter this system by capping the amount of awards one principle investigator can receive at $1.5 million.

And while I suspect you will state this proposal will only scrutinize large guarantees and not mandate a strict dollar-level cap, I'm concerned that there's a larger issue with this proposal; that is, a disincentive to success.

This proposal limits the amount of rewards one investigator can receive through the peer-review process and does not let science dictate funding decisions.

Dr. Collins, what will make a researcher strive for the next discovery when they're limited in the awards that they can receive? Could you explain?

Dr. COLLINS. Senator, I appreciate the question very much, and we are, at NIH, proud of being what we would call ourselves a meritocracy; that is, you get supported by NIH because of the strength of your science.

Senator SHELBY. Right. Well, that's a strength of NIH, isn't it?

Dr. COLLINS. It is. And we aim to maintain that.

This circumstance is born of the particularly difficult constraints that we now see in front of us, where there is no magical solution to the several pressures.

I mentioned earlier that the ability of early stage investigators who are just getting started to get funded is clearly putting them under considerable stress.

We debated over many months whether in fact there were levers that NIH might be willing to try to pull in this circumstance to be sure that we were supporting the best science in a way that might require a little bit more scrutiny in certain circumstances.

And you're right in your comment. What we are not proposing is a cap on an individual investigator's support at $1.5 million, not at all. It is just that if an investigator has already achieved that amount of funding and comes in asking for more, that particular grant is going to get a little bit more scrutiny to be sure that this is in fact the best use of the taxpayers' dollars.

That's what we're aiming to try to do. This has been, in some ways, piloted by National Institute of General Medical Sciences (NIGMS). They have been doing this already for several years, and even at a lower cap, at $750,000.

And most of the time, when they look at the application, they said, this is great science, we should fund it. We've looked at it a little bit more closely now. We want to be sure that this investigator can actually manage three or four projects as opposed to one, and we think they can, and let's go ahead and see what they can do.

Senator SHELBY. So you're not saying you're going to cap it?

Dr. COLLINS. No.

Senator SHELBY. You're going to measure it and see what happens.

Dr. COLLINS. We're going to look at it a little more closely and see what happens.

Now only about 6 percent of our investigators are at that level, so this is not going to clog the system. And it will be the decision of our advisory councils, who are themselves very invested in the

meritocracy model, who will decide whether, in fact, this is the right place to go.

REPLICATING RESULTS

Senator SHELBY. In December, the Wall Street Journal ran a front-page article entitled, "Scientists' Elusive Goal: Reproducing Study Results." I'm sure you saw that.

The article described a phenomenon in which most biomedical study results, including those funded by the NIH, that appear in top peer-reviewed journals cannot be reproduced or replicated.

The article cited a Bayer study, describing how it had halted 64 percent of its early drug target projects because in-house experiments failed to match claims made in the publications.

This is a great concern, Dr. Collins. I don't want to ever discourage scientific inquiry, and I know you don't, or basic biomedical research. But I think we on this subcommittee, we need to know why so many published results in peer-reviewed publications are unable to be successfully reproduced.

When the NIH requests $30 billion or more in taxpayer dollars for biomedical research, which I think is not enough, shouldn't reproducibility, replication of these studies, be a part of the foundation by which the research is judged? And how can NIH address this problem? Is that a concern to you?

Dr. COLLINS. It certainly is, Senator. And that Wall Street Journal article also I think raised many ripples of concern, because of the numbers that Bayer was citing.

Well, first of all, we know that investigators who are doing cutting-edge science are working in areas where you're at the edge of what's possible.

Senator SHELBY. We know you're experimenting and you're hoping. I understand.

Dr. COLLINS. Exactly. And so it is not surprising that in that circumstance you may come up occasionally with results that others can't seem to replicate but——

Senator SHELBY. What about that kind of percentage?

Dr. COLLINS. Well, the percentages quoted by Bayer were certainly deeply troubling.

Senator SHELBY. What about at NIH? What kind of percentages do you have there?

Dr. COLLINS. I think it would depend on exactly how the question was phrased. So certainly——

Senator SHELBY. What do you mean by that?

Dr. COLLINS. Well, when somebody is publishing a paper saying that we have determined that it is exactly 24.3 percent of individuals who have a particular problem when it turns out it's really 31 percent or 17 percent. Well, was that a confirmation or not? You see the issue in terms of the precision.

Bayer as a company is trying to make drugs. They want to tolerate no imprecision before they invest hundreds of millions of dollars. So, some of this is along those lines.

Senator SHELBY. Okay.

Dr. COLLINS. Some of it is, frankly, the fact that when you try to repeat an experiment, you may not do it exactly the same way. And both answers could be right, the original investigator and the

person who tries to reproduce it, but they actually didn't quite do the same experiment. And that is always a possibility when you look at a conflict of this sort.

But you know what the good news is? It's that science is self-correcting, that over the course of time, any result that matters is going to be looked at by other investigators, in the private sector, in the public sector. And if it is not correct, you will discover that relatively soon. And if it is correct, others will know that and will build upon it.

So despite the concerns here, which I think are quite real, I think we can be confident that our overall scientific foundation is strong.

Senator SHELBY. Thank you. Thank you, Mr. Chairman.

Senator HARKIN. Great response.

Senator Mikulski.

FEDERAL EMPLOYEES: RECRUITMENT AND RETENTION

Senator MIKULSKI. I know the hour is growing late, and I want to note Senator Harkin's concern about prevention.

And when we did the Affordable Care Act, this was going to be one of the lynchpins of our bill, both prevention and quality initiatives, so that we can both save lives, improve lives, as well as save money.

That is why we looked at chronic conditions. That is why you'll hear me talk so much about them. The epidemic that we know is a chronic condition. Hopefully, one day we can manage Alzheimer's the way we manage diabetes, that we know that it is there, but we can handle it.

Unfortunately, the prevention money has been used as a bank to fund other things, and this is what has Senator Harkin so concerned and, quite frankly, myself.

And I think we need to look at the Alzheimer's funding. We need to talk about where else we can look to that, because it would be a sad day in our country where one important need and one important paradigm shift and focus is pitted against each other. So we look forward to working together to solve this problem and to move ahead.

But I want to talk about Federal employees in your NIH. Of course, I am deeply concerned about the continual attack. Not only do we have to look at how we are going to fund Federal employees, their pay, their pensions, the pay freeze but also this ongoing hazing, harassment, snarky comments, throwaway one-liners, and so on.

Now that's how I feel. Could you tell me, Dr. Collins, how that impacts your recruitment and retention? Or have I just got a soft heart towards Federal employees?

Dr. COLLINS. We thank you for your soft heart, Senator. It means a lot.

But this is a very serious issue in terms of morale. For individuals like the 18,000 who work at NIH, to read about themselves in the comments of individuals who've never met anybody who works at NIH and who talk about these being employees who are simply overpaid and contributing little is deeply hurtful.

I am so proud to stand at the helm of an organization with such incredibly dedicated people, some of whom you see here at this table with me, and all of those, in terms of senior scientific positions, who could easily be employed at much better financial rates in other parts of the public and private sectors, and who are doing this work because of their hopes of making a difference, because of their public spirit, because of their determination to make the world a better place.

To have that kind of dedication characterized in the way that seems to be done in a sweeping way by people talking about Federal employees as if they are somehow a parasite upon the public is really deeply hurtful.

And of course, that is translated into decisions in terms of ways in which Federal employees are being treated in terms of financial aspects, which I think our employees are ready to actually tighten their belts and take whatever needs to be done in an honorable fair-minded way, as far as helping out with the difficulties our Government faces.

But why gang up on them? Why try to single them out?

Senator MIKULSKI. Here is my question in line with that. Since all of the activities that have been going on, particularly around pensions, extended pay freezes, and so on, do you see an upsurge in requests for retirement?

Dr. COLLINS. I don't know if I have statistics on exactly——

Senator MIKULSKI. I am not only talking about the Ph.D.'s, but we're talking about the lab people, the ones who run that fire department. I mean, there is a lot of support staff that goes on to enable the scientist to be the scientist.

Dr. COLLINS. Indeed. And we depend on those people critically or we couldn't do our work. I don't know whether there is an actual statistical indication of an upsurge in retirements, but certainly as an indicator of general morale, I would not be surprised if that is the case.

And when it comes to your other question about hiring people, the kinds of hires that I am trying to be involved in generally are the high-level senior scientists, and this question comes up, "Is this a good time to come and work for the Federal Government? All the things we are reading about in the paper makes it sounds as if we're not going to be considered as the leaders we hoped to be." It is a serious issue.

Senator MIKULSKI. So my colleague from the other side asked excellent questions about, you know, the issues about the availability of scientists, are they going elsewhere to do research, should we change our immigration policy, give every new Ph.D. a green card? Those are subjects of debate. But we are losing out on ourselves, aren't we?

Dr. COLLINS. We are. Even for the people that grew up here and want to stay here. They are not necessarily being well-received, as they should be for their dedicated service.

Senator MIKULSKI. Right. And as I look at the table, I note the longevity and the incredible service, Dr. Hodes, we've known. Dr. Fauci I have known from more than 25 years—20 years.

Dr. COLLINS. I bet its 25 or 30 years.

Senator MIKULSKI. I bet that.

And Dr. Varmus was at NIH, left for Memorial Sloan-Kettering Cancer Center, came back to head a new Institute. This says something about mission-driven. But I think we need to correct it.

Now, I want to be clear, I don't have my coat on as symbolic defiance of the pay freeze.

But I think we need to not only look at how we can manage our Government in a more frugal way, but I think we need to stop this bashing of our Federal employees, and, like you said, take note of what we ask them to do. Everybody is against the Federal employees until they want them and need them.

Dr. COLLINS. Thank you, Senator.

Senator MIKULSKI. Thank you very much.

NATIONAL INSTITUTES OF HEALTH FUNDING

Senator HARKIN. Thank you, Senator Mikulski.

I just want to clear up—maybe I misspoke or I may have left a wrong impression when I said that we won't take money from the prevention fund for NIH; we won't take from the NIH for the prevention fund.

That is not necessarily true. It depends on what it is being used for.

For example, Dr. Rodgers, we have the NIH fund for the diabetes prevention program. In fact, I included $10 million from the PPHF for that, because that is a proven intervention. It has been proven to prevent and to delay the onset of type 2 diabetes.

The research for that, however, was funded both by NIH and CDC collaboratively. So once they have funded the adequate research, and they have proven interventions, that is where we're more than willing—I am more than happy to get money out for the prevention aspects of that.

What I was talking about on Alzheimer's is that the research for Alzheimer's should not come from the PPHF. If your research leads to some proven preventative measures, which we hope it does, then that is the point at which then we step in with the PPHF. Do you see what I'm saying?

So I just want to kind of clear that up. That's why the $80 million is not going to happen from us. If you've got a proven prevention strategy that has been proven through research, fine. That's what the Prevention and Public Health Fund is for. I just want to clear that up.

BIOLOGY OF AGING

But one other question, Dr. Hodes, on Alzheimer's. As to the question about the biology of aging, when we think of Alzheimer's, cancer, congestive heart failure as distinct diseases, one thing they have in common, it comes with aging. And so if we can learn more about the aging process, we think that might give us more insight into this.

The NIA took the lead in establishing a group to coordinate efforts across the NIH on understanding the role aging plays in susceptibility to age-related diseases.

Can you just tell us a little bit more about the current activities of this interest group and why is it important?

Dr. HODES. Thank you for that question, and I would be happy to.

Just as you described, aging is clearly a risk factor for many of the changes, diseases, conditions that occur as the years go by. And there is increasing evidence that there are identifiable, underlying biological processes that occur with aging that may be of interest not only in their own purely scientific right, but because they give clues as to points of intervention to affect many of the conditions with aging.

With this in mind, with increasing evidence, exciting studies such as a recent demonstration that in experimental animals, small numbers of cells which can be identified as senescent—they behave abnormally; they secrete abnormal proteins; but they are in very small numbers—went through very ingenious genetic manipulations. They are removed from a live animal, a mouse model. The mouse does better. The mouse has reversed many of the conditions that occur with aging, as an example of the way that intervening at this basic level may have broad implications.

Based on this kind of conviction, there has been over the past several months discussions beginning with a number of us at the table here as Institute Directors, a support of an interest group that brings together those who may have primary affiliations with various disease organ-centered Institutes and Centers, but in common have reason to believe that the underlying aging process is relevant to all of us.

This interest group now has sponsored and will continue a series of lectures, of journal clubs. But most importantly, it creates a new forum for looking at ways in which common support from across the NIH toward problems that are appropriately targeted for the benefit of all us based on the condition of aging will benefit—and it is truly an exciting time and a revolutionary kind of expansion in the way this consciousness now has progressed across NIH.

So we're very excited by it. We think it has great promise for making our research more efficient, more targeted to serve all.

Senator HARKIN. Very good.

I have agreed to permit this room to be used by the National Alliance on Aging after this hearing for a press conference on that subject.

There was one other thing I wanted to bring up here. I have a lot of things I would like to bring up here, as a matter of fact.

I am down to 15 seconds. Do you have another question that you want to ask?

Senator Mikulski.

Senator MIKULSKI. I think that's it.

Senator HARKIN. Do you want anything else?

I'll tell you what, I'll submit it in writing. It is a longer question. I'll submit it in writing. We're getting close to the noon hour anyway. It has to do with the tension between more grants for less money, fewer grants for more money. We kind of touched on that in the beginning. I would like to delve into that a little bit more, and I'll do it with a written question, just how you're looking at that tension that is going on, because we want to increase the grants but decreasing the amount of money, what does that do?

Anyway, I am conflicted by it. I don't know what the right answer is. So I'll write it to you.

Anything else that anybody wanted to bring up for the record that we not have asked or you wanted to follow up for any clarification purposes or anything like that? Anyone at all?

ADDITIONAL COMMITTEE QUESTIONS

Well, listen, our thanks to all of you for your great leadership at the NIH, and we're going to do our best to make sure that our budget is not only not decreased, but we hopefully increase it a little bit, but things are tight around here, as you know.

Senator SHELBY. Especially in the area of biomedical research.

[The following questions were not asked at the hearing but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

NUMBER OF NEW GRANTS

Question. Dr. Collins, you noted in your opening statement that the number of new and competing research grants in the President's budget would rise from 8,743 in fiscal year 2012 to 9,415 in fiscal year 2013, an increase of 672. That's encouraging. But to achieve this increase, the value of individual grants would drop slightly. As you explained, noncompeting grants would be cut by 1 percent.

This raises a fundamental dilemma for National Institutes of Health (NIH), one that is likely to persist as long as budgets remain tight. And that is: Is it better to award more grants for less money or fewer grants for the same (or more) money?

The President's budget seems to have opted for the former approach. More grants mean a higher success rate, plus more opportunities for young researchers to win their first award. But of course there are also disadvantages when the average value of each grant drops. Some argue that it makes more sense to simply fund the best science, and if that means fewer grants, then so be it.

Please comment on this tension and why the President's budget puts an emphasis on increasing the number of grants.

Answer. NIH uses its Research Project Grants (RPG) to support the most meritorious research applications identified by a rigorous peer-review process to have the highest potential for advancing biomedical knowledge and public health. The total number of competing RPG estimated in the President's fiscal year 2013 budget request is expected to increase to 9,415 compared to the 8,743 funded by the fiscal year 2012 enacted level. A tight budget environment prompts a delicate balancing of needs to fund adequately new individual projects, support the maximum number of new research opportunities, and sustain existing grants. In order to maximize resources for investigator-initiated grants, NIH plans to follow grants management policies in fiscal year 2013 that discontinue outyear inflationary allowances for most grants. In the short term, NIH plans to reduce noncompeting continuation grants by 1 percent less than the fiscal year 2012 level, and negotiate the budgets of competing grants to avoid growth in the average award size. In the future, sound fiscal management requires that we continue to carefully consider the number, cost, and duration of new RPGs in order to minimize negative impact on existing programs.

Accompanying these policies for maximizing resources in fiscal year 2013 for new investigator-initiated grants is our continued commitment to award grants to new investigators at rates equal to those of established investigators. Also, NIH will establish a new process for additional scrutiny of awards to any principal investigator with existing grants of $1.5 million or more in total costs by an Institute or Center's Advisory Council. The purpose of this policy is to promote the award of NIH research grants to as many distinct principal investigators as possible.

These policies will work in concert to ensure that pursuit of new research questions, the lifeblood for cutting-edge science, is maintained. Science advancement includes both the production of new knowledge and new scientists. New scientists, however, must have a reasonable expectation that they will be able to successfully compete for their own research grants at the end of their prolonged period of training if they are to be retained as members of the biomedical research workforce. NIH has strategically chosen in fiscal year 2013 to support a larger number of new re-

search project grants by sustaining support for noncompeting continuations at 99 percent of their competing levels. This approach balances NIH's commitment to its ongoing research portfolio with the need to stimulate new research ideas and priorities in this time of limited resources.

NATIONAL CHILDREN'S STUDY

Question. Dr. Collins, NIH, Centers for Disease Control and the Environmental Protection Agency spent a combined $54.7 million on the National Children's Study (NCS) from fiscal year 2000 through fiscal year 2006. From fiscal year 2007 through fiscal year 2012, the Congress appropriated another $937 million for the NCS, bringing the total to almost $1 billion. What has this nearly $1 billion achieved so far?

Answer. NIH has shown the feasibility of performing an NCS by designing and testing varied scientific approaches and demonstrating how to conduct a study of this size and scientific and logistical complexity in a fiscally sound manner.

In addition to comparing different enrollment strategies to develop a scientifically valid and fiscally responsible methodology to enroll 100,000 children in the Main Study, the NCS has enrolled more than 3,000 children to date in the Vanguard Study. In addition, we have developed innovative approaches to research methodology and developed broadly useful research tools.

Examples include:

—New informatics approaches including:
  —The capacity to capture systematically the operational, logistical, and cost data for an ongoing study;
  —A comprehensive approach to harmonize the terminology for neonatal medicine, including the deposition of hundreds of terms that researchers around the world can use into the National Cancer Institute Enterprise Vocabulary Services;
  —Development of nonproprietary data collection, case management, and data archiving tools that conform to international data standards and can be used in many types of research;
  —Development of a system of tagging data to allow rapid analysis and data pooling for research data;
  —Simulation strategies for comparing complex recruitment strategies; and
  —New methods for implementing and analyzing recruitment in large studies and an analytic approach to examine rates, kinetics, and efficiencies to allow selection of optimal recruitment strategies;
—A research portfolio of approximately 300 individual studies, most of which were multicenter, to establish and validate methods to support the Study;
—In conjunction with the U.S. Department of Health and Human Services Office for Human Research Protections, a national network of Institutional Review Boards using a Federated Model that covers all 36 National Children's Study Centers, which saves time and costs for administrative review for human research protections;
—A biobank repository for human biological specimens and environmental samples that is modular and scalable. The repository has collected about 125,000 specimens and has already distributed thousands of specimens for analysis and additional scientific projects;
—A research workflow process in 40 locations that is flexible and cost effective that can be used by many other types of research, as well as the NCS. For example, the Clinical and Translational Science Awards (CTSA) Consortium is adapting the same processes in many of the 28 NCS locations that are also CTSA locations;
—Collaborations with longitudinal birth cohort studies around the globe to harmonize practices and leverage resources; and
—In collaboration with other statistical agencies, new statistical methods for analysis for combining data from multiple types of research.

Question. The President's budget for fiscal year 2013 would add another $165 million. What do you estimate the cost of the NCS will be in fiscal year 2014, when recruitment is expected to begin?

Answer. Pilot testing conducted through the NCS Vanguard sites showed that a study design based on recruiting participants through healthcare providers was most efficient. Other large Federal studies have also effectively employed this provider-based approach. Also, while the revised approach may use healthcare provider networks as the primary source for recruitment, the NCS could see additional participants through secondary sources (such as title V clinics, Indian Health Service clinics, or contract research organizations) to assure inclusion of all appropriate pop-

ulation groups. The President's budget request for fiscal year 2013, which shows a reduction of approximately 15 percent to $165 million for the NCS, appropriately reflects these proposed design changes. While future funding needs for the outyears will be determined by early data gathered by the Main Study, we anticipate that the budget for fiscal year 2014 will be the same as for fiscal year 2013.

Question. How long will the recruitment phase take, and do you expect the annual cost will remain fairly constant during that period?

Answer. We expect to issue the Request for Proposals for the Main Study in the fall of 2012, with awards made in 2013 and recruitment beginning in 2014. The recruitment phase is expected to continue for approximately 3 to 3½ years. We anticipate annual costs will remain flat in unadjusted dollars during the recruitment phase.

The NCS is able to reduce overhead costs through greater operational efficiencies and redistribution of tasks and responsibilities. Examples include the use of nonproprietary software to eliminate license fees and proprietary support; use of a federated model for human subject protection to reduce redundancy and speed approvals through elimination of duplicate administrative resources; use of the NCS Program Office as a coordinating center to develop study instruments and protocol documents, to perform data analysis, and to manage field operations and general consolidation of overlapping field operations.

With the reduction in overhead, we anticipate that for fiscal year 2013 we need approximately $35 million for support services and $130 million for ongoing Vanguard operations and Main Study initiation. Main Study initiation includes:

—community outreach and advertising;
—memoranda of understanding with cooperating facilities;
—establishment and testing of informatics platforms, including data security and regulatory compliance;
—establishment and testing of biospecimen and environmental sample collection and shipping from study locations;
—training of field personnel;
—regulatory approvals for information collection from participants; and
—establishment of data collection and transmission quality assurance and quality control processes.

Question. Is the annual cost expected to rise or decline after the recruitment phase? If so, by approximately how much (e.g., 25 percent)?

Answer. Once the more labor-intensive recruitment phase has been completed, funding requirements for the NCS over the life of the study are expected to remain stable. While the number of participant visits each year may decrease to once per year, some subgroups in the Study may receive additional questionnaires on specific topics. In addition, as the number of biospecimens and other data collected from Study participants increases, the fiscal needs of the biobank and data warehouse rise, as these data and samples are both stored and made ready for analysis by other scientists.

Question. Do you expect the annual cost will remain fairly constant during the Main Study, once recruitment has been completed?

Answer. Annual unadjusted costs are expected to remain constant in unadjusted dollars following the recruitment phase of the Main Study. The prenatal and infant development phases are of critical importance because of the potentially long-term effects of various environmental exposures; consequently, the NCS plans to "frontload" the Study, conducting more participant visits and sample collections in those years. However, as the frequency and intensity of study visits decreases, the costs associated with biospecimen and environmental sample processing, storage, and analysis and with data processing, storage, analysis, and security will increase.

PAIN RESEARCH

Question. Dr. Collins, I understand that National Institute of Neurological Disorders and Stroke plans to establish a new trans-NIH working group on overlapping chronic pain conditions. Please provide some more details on this effort and what it is intended to accomplish.

In addition, what mechanisms will the NIH employ to:

—expedite scientific understanding of the factors that predispose, trigger, and perpetuate chronic pain;
—advance our knowledge of the diverse underlying mechanisms responsible for chronic pain (including individual differences and sensitivity to pain);
—identify promising effective therapeutic drugs (and other approaches) for pain control; and

—expedite the translation of these findings to those suffering, especially the most at-risk populations such as women?

Answer. In 2011, NIH hosted a number of meetings and workshops focusing on overlapping chronic pain conditions that disproportionately affect women. These workshops included discussions of possible common pathways underlying these conditions as well as the need for improved research diagnostic criteria for overlapping pain conditions. To address these issues further, a new trans-NIH overlapping chronic pain conditions working group was formed in fall 2011. The group is led by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Dental and Craniofacial Research and brings together staff from 13 Institutes and Centers involved in pain research as well as a representative from the patient advocacy community. The working group will help coordinate research efforts across the NIH on overlapping chronic pain conditions and is planning a trans-NIH conference in August 2012 that aims to:

—evaluate and summarize current knowledge on the causes and progression of overlapping pain conditions;

—identify critical research needs, such as improved research diagnostic criteria for this group of conditions; and

—enhance interdisciplinary collaboration and cooperation in this area of research.

NIH utilizes a number of mechanisms to fund research on understanding the factors that predispose, trigger, and perpetuate chronic pain and the underlying mechanisms responsible for individual differences and sensitivity to pain. Sixteen NIH Institutes and offices supported the NIH Blueprint for Neuroscience Grand Challenge on Pain, whose goal was to facilitate highly collaborative, multidisciplinary research to better understand the mechanisms that underlie the transition from acute to chronic pain. Research supported by this initiative aims to understand the important role of neuroplasticity—or changes in the nervous system—in transitioning to chronic pain and the need to reverse these maladaptive changes, to allow recovery. Other projects funded through this initiative are focused on the identification and modulation of genetic changes that predispose individuals to and contribute to the onset of chronic pain. NIH continues to accept competitive revisions that propose a collaborative, 1-year pilot study or new specific aim associated with an active NIH grant as part of this initiative. The Mechanisms, Models, Measurement and Management in Pain Research Initiative supported by 11 NIH Institutes is another example of a trans-NIH solicitation that encourages a wide range of basic, translational, and clinical research on pain including sex differences in the pain experience and genetic contributions to individual variability and response to treatment.

The pain portfolios at a number of NIH Institutes include research focused on risk factors for chronic pain and individual differences in pain perception. For instance, brain imaging studies (fMRI and resting state fMRI) supported by NIH have compared structural and functional brain changes with pain states, supporting the notion that central nervous plasticity is a characteristic of chronic pain. A cutting-edge study used cortical imaging to detect changes in the brain to distinguish which patients transition from acute to chronic back pain and which recover. Extensive use of imaging tools have also shown that differences in patient reported pain sensitivity are correlated to activation of brain regions associated with pain and are linked to sex, race, genetic makeup, and environmental stress levels. Environmental factors such as hormones and stress have been shown to contribute to differences in pain sensitivity and analgesic response, while genetic variants determine individual sensitivity to certain analgesics, ability to sense pain, and risk for chronic pain. Preliminary results from the NIH-supported Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study have helped identify several genetic markers associated with risk for orofacial pain and related to different patterns of self-reported pain. NIH is also funding the ongoing Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) studies to study pain characteristics that contribute to risk for transition to chronic pelvic pain and a 10-year study on overlapping pain conditions that disproportionately affect women, including episodic migraines.

In addition to funding basic research on underlying mechanisms and causes for chronic pain, NIH supports a number of activities to advance the development of therapies to control and alleviate pain, including multiple activities in partnership with the FDA. Members of the NIH Pain Consortium—a joint undertaking across 25 NIH Institutes, Centers, and offices that facilitates collaborative pain research—currently participate in an advisory committee for the Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) Initiative, a public-private partnership program sponsored by FDA to streamline the discovery and development of analgesics. In May 2012, NIH and the Federal Drug Administration plan to hold a state of the science workshop on assessing opioid efficacy and

analgesic treatment in conjunction with the seventh annual NIH Pain Consortium Symposium focusing on advancing pain therapies. More broadly, senior leadership from the NIH and FDA are involved in an NIH–FDA leadership council that is exploring better coordination of NIH and FDA efforts to improve regulatory science and overcome hurdles in the drug development pipeline for common and rare diseases.

The NIH Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program supports research on developing pain therapies including projects focused on:

—the development of small molecules as anti-inflammatory, analgesic agents;
—neural stimulation to relieve phantom limb pain;
—Internet tools for self-management as an adjunct to chronic pain care;
—improved opioid formulations with fewer side effects; and
—selectively targeting pain nerve fibers for gene delivery.

NIH continues to encourage applications through the SBIR program, Institute-specific translational programs, and other mechanisms including trans-NIH initiatives. For example, the NIH Blueprint for Neuroscience Research currently supports a Grand Challenge for Neurotherapeutics to address the lack of effective treatments for disorders of the nervous system, including chronic pain. Additionally, the newly established National Center for Advancing Translational Sciences (NCATS) at NIH will catalyze the generation of innovative methods and technologies to enhance therapy development for a wide range of human diseases and conditions.

NIH is currently involved in diverse dissemination efforts to inform the public about pain research findings. NIH is a member of the new Interagency Pain Research Coordinating Committee (IPRCC) which was recently created under the Affordable Care Act to enhance pain research efforts and promote collaboration across the government, with the ultimate goals of advancing fundamental understanding of pain and improving pain-related treatment strategies.

The subcommittee has been specifically charged with making recommendations on how to best disseminate information on pain care, and NIH is working together with other member Federal agencies to collect information on current dissemination efforts in order to inform these recommendations.

The NIH Pain Consortium is encouraging medical, dental, nursing, and pharmacy schools to respond to a new funding opportunity to develop Centers of Excellence in Pain Education (CoEPEs). The CoEPEs will act as hubs to develop and disseminate pain management curriculum resources for healthcare professionals and provide leadership for change in pain management education. Additionally, NIH provides online informational material on numerous chronic pain disorders that specifically reference overlapping pain conditions, and funds grants testing methods to teach patients how to access high-quality web-based health information for self-management of pain.

FOOD ALLERGIES

Question. Dr. Fauci, life-threatening food allergy conditions affect millions of America's children. Trials in a small number of patients have demonstrated that oral immunotherapy (OIT) is safe and effective in a significant percentage of patients. Many researchers believe the next step is to determine the most effective dosage and timeframe for treatment through larger and more complex clinical trials. As we both know, however, these trials are expensive. While there are indications of substantial private philanthropic support, Federal money will also be required. One private research group has estimated that the cost of phase II trials for the eight major food allergens (peanut, tree nut, milk, egg, soy, wheat, fish, and shellfish), along with mechanism and longitudinal studies, would total about $90 million over 6 years.

Answer. The National Institute of Allergy and Infectious Diseases (NIAID) is conducting Phase I and II clinical trials to evaluate OIT or sublingual immunotherapy (SLIT) to treat or prevent food allergy. These clinical trials include studies of various immunologic parameters to understand factors that relate to the development or natural resolution of food allergy and/or response to therapy. Recent and ongoing NIAID-sponsored OIT and SLIT trials include:

—phase II clinical trial that showed that egg OIT is safe and effective in children 5 to 18 years old with egg allergy (in press, New England Journal of Medicine);
—phase I/II clinical trial to determine whether peanut extract placed under the tongue (SLIT) is a safe and effective treatment for adolescents and adults with peanut allergy;
—phase II clinical trial of milk OIT combined with anti-immunoglobulin E (omalizumab) for the treatment of children with milk allergy;

—phase II clinical trial to determine if regular consumption of baked foods containing milk will enable children with milk allergy to drink milk and consume milk-containing foods; and
—phase I/II prevention trial in which infants and young children at high risk for peanut allergy regularly consume peanut-containing snacks to determine if this will prevent the development of peanut allergy by age 5–6 years.

Several OIT trials also are in development for children (1–4 years of age) and adults with peanut allergy.

A few additional studies, conducted without NIH sponsorship, have recently been published. Similar in size to the NIH-sponsored studies, these phase I/II clinical trials (typically 20–60 children per study) have focused on milk, egg, and peanut and lead to similar conclusions, i.e., approximately 60–90 percent of those subjects who remain on OIT for 1–2 years can tolerate modest amounts of the food.

Question. Are you in general agreement that the scientific studies already completed on OIT indicate that moving ahead with larger trials on key allergens is appropriate at this time?

Answer. NIAID is enthusiastic about recent results of OIT for milk, egg, and peanut and agree that it will be important to proceed with larger phase II trials for these and other food allergens. While we anticipate many similarities in study design, the most promising approaches will likely differ based on the particular allergen and study populations (e.g., children vs. adults; mild vs. severe disease; treatment vs. prevention design; and single vs. multiple food sensitivities).

Although OIT is currently the most promising approach for treating food allergy, a small number of patients appear not to respond to OIT and others (10–20 percent) are unable to tolerate OIT because of recurrent allergic reactions. Furthermore, patients with a history of severe anaphylaxis, who are most in need of new treatment strategies, have not been enrolled in these early-stage OIT clinical trials due to safety concerns. Further research is necessary to develop and test treatment strategies that will benefit these patients. Novel treatment strategies may also provide improved safety and efficacy for food allergic individuals in general. For example, the addition to OIT of an anti-immunoglobulin E or similar molecule may reduce adverse effects of OIT and allow for larger doses of OIT that might be more effective. Other routes of allergen administration, e.g., via a cutaneous patch, should also be explored.

Question. What is your professional judgment as to the cost and appropriate timing of such a system of trials?

Answer. For OIT that involves administration of a food alone (e.g., milk, egg, and peanut), large phase II studies may be sufficient to change clinical practice (foods are not licensed by the FDA as therapeutics). Nonetheless, many such studies would be comparable in scope, complexity and cost to modest size phase III clinical trials required for drug licensure. In contrast, full phase III licensure studies will be required if OIT is combined with pharmaceuticals or allergen immunotherapy is administered through devices such as a cutaneous patch.

In our professional judgment, a prioritized set of clinical trials would include:
—a series of larger phase II studies to confirm the promising results of the studies on egg, milk, and peanut outlined previously (estimated cohort sizes of 100–300 subjects);
—phase II/III studies of OIT for the same allergens with the addition of pharmaceuticals (e.g., anti-immunoglobulin E) to diminish adverse events in OIT and improve efficacy of OIT;
—phase I–III studies of peanut (and perhaps other food allergens) delivered by cutaneous patch;
—phase I/II pilot studies exploring OIT for the other major food allergens (tree nut, soy, wheat, fish, and shellfish) followed by larger phase II studies (100–300 subjects) to confirm any promising results; and
—various food allergy prevention trials in high-risk infants and young children. We anticipate that the minimum duration of most phase II–III trials would be 3–4 years and most prevention trials would take 6–7 years.

To ensure that the highest-priority studies are conducted ethically, rigorously, and safely, such studies should be phased in over a period of years. A phased process will allow knowledge gained from the initial studies to inform the design of future studies, improve safety, and enable cost efficiencies.

Factors that contribute to total costs include cohort size, study duration, complexity of treatment regimens and clinical outcomes, the number of protocol-required blinded food challenges, costs of allergen preparation and distribution under Good Manufacturing Practices, costs of additional pharmaceuticals (e.g., biologics, such as monoclonal anti-immunoglobulin E or cutaneous patch delivery devices), and the type and number of immunologic parameters to be studied. Thus, in our professional

judgment, an integrated set of a prioritized set of clinical trials could cost $150–$250 million over many years. Additional constraints on implementation of such a highly ambitious set of clinical trials include the limited capacity of academic research centers and the relatively small existing cadre of highly trained and experienced adult and pediatric specialists in food allergy research.

Question. How much money would be required in the first year to initiate a full set of OIT trials?

Answer. NIAID would recommend that a full prioritized set of OIT clinical trials as outlined above not be initiated in a single year. We estimate a first-year total cost of $20–$25 million to fund four of the highest priority OIT clinical trials for peanut, egg, and/or milk allergens.

QUESTIONS SUBMITTED BY SENATOR DANIEL K. INOUYE

INSTITUTIONAL DEVELOPMENT AWARD (IDEA) PROGRAM

Question. Over the past 13 years, the Congress has supported the National Institutes of Health (NIH) Institutional Development Award (IDeA) program. In IDeA States like Hawaii, our biomedical communities have seen great improvement in our scientists' ability to garner NIH support as well as our capacity to recruit and retain biomedical scientists, physician-scientists, teachers, graduate students, and postdoctoral fellows. With the dissolution of the National Center for Research Resources (NCRR), which administered IDeA, and the proposed budget reduction of IDeA by $50 million (representing an 18-percent cut), there is concern that NIH is not fully committed to the IDeA program even though the Congress has been supplementing the IDeA budget for the purpose of expanding clinical translation research efforts in IDeA States. What assurances can you provide that NIH supports the IDeA program and will continue to sustain research infrastructure support targeting the chronically underfunded IDeA States?

Answer. Following the dissolution of NCRR, the IDeA program was transferred to the National Institute of General Medical Sciences (NIGMS), a logical home in view of NIGMS' long-standing commitment to research training and capacity building. Nearly all the NCRR staff who managed the IDeA program also moved to NIGMS, enabling the administration of the IDeA grants to proceed seamlessly.

NIGMS is strongly supportive of the IDeA program. NIGMS appreciates its value to States that do not receive high levels of support from NIH's traditional grant mechanisms, as well as its importance in enabling excellent research, training, and career development that benefit the entire Nation. NIGMS intends to essentially maintain the level of support for the Centers of Biomedical Research Excellence (COBRE) and IDeA Networks of Biomedical Research Excellence (INBRE) programs and the new Clinical and Translational Research program.

HEALTH DISPARITIES

Question. Given the continuing disparities in health outcomes and NIH's acknowledgement of the low numbers of underrepresented minority researchers, please describe efforts to address disparities in health outcomes and the representation of minority investigators in NIH support research programs.

Answer. While the overall health of the U.S. population has improved, certain populations continue to have a higher risk of adverse health outcomes. These health disparities are the result of multifactorial biologic and nonbiologic influences. The NIH Health Disparities Strategic Research Plan and Budget, a 5-year plan, provides a blueprint for addressing health disparities and fostering access of racial/ethnic minorities to the clinical benefits of NIH research. The Plan focuses on three major goals each NIH Institute and Center must strive to achieve:

—conduct and support research on the factors underlying health disparities;
—expand and enhance research capacity to create a culturally competent workforce; and
—engage in proactive community outreach, information dissemination, and public health education.

The pace of translation is a recognized barrier to racial/ethnic minorities reaping the benefits of clinical research. NIH is committed to accelerating the pace of research translation by reducing the time it takes for scientific discoveries to reach patients in the form of treatments or health information. Several ongoing research programs and studies contribute to the NIH efforts to translate research findings to racial/ethnic communities and increase their access to the benefits of NIH-funded research, including the following:

Development and Translation of Medical Technologies That Reduce Health Disparities Initiative

National Institute on Minority Health and Health Disparities (NIMHD) and the National Institute of Biomedical Imaging and Bioengineering established a partnership through the Small Business Innovation Research program to support the development and translation of medical technologies aimed at reducing disparities in healthcare access and health outcomes. Potential technologies targeted are telehealth for remote diagnosis and monitoring, sensors for point-of-care diagnosis, devices for in-home monitoring, mobile, portable diagnostic and therapeutic systems, devices which integrate diagnosis and treatment, diagnostics or treatments that do not require special training, devices that can operate in low-resource environments, non-invasive technologies for diagnosis and treatment, and integrated, automated system to assess or monitor a specific condition.

National Institute on Minority Health and Health Disparities Community-Based Participatory Research Initiative

This 11-year initiative is designed to facilitate the translation of scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce health disparities and to disseminate scientific information. These Community-Based Participatory Research (CBPR)-supported intervention studies are expected to enhance clinical practice and improve the health of racial/ethnic populations by actively engaging the community in all phases of research including design, implementation, and dissemination of the research results.

National Institute on Minority Health and Health Disparities Centers of Excellence Program

The Centers of Excellence (COE) program advances scientific knowledge on the biological and nonbiological factors contributing to health disparities and develops interventions to address some of the most prevalent diseases, and health conditions that disproportionately affect racial/ethnic minority populations. Since 2002, NIMHD has supported 91 COE sites in 35 States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. Awardees represent all types of institutions including Historically Black Colleges and Universities, Hispanic Serving Institutions, Tribal Colleges and Universities, and Alaska Native and Native Hawaiian Serving Institutions.

Although NIH recognizes a unique and compelling need to promote diversity in the biomedical, clinical, behavioral, and social sciences research workforce; sufficient representation has been to date elusive. Advancing diversity through NIH training support is expected to produce a number of tangible and overlapping benefits including:

—enhancing the overall capacity to address health disparities;
—improving patient satisfaction in ways that enhance participation in clinical research setting; and
—creating and preparing a culturally competent workforce that enhances communication.

Research Supplements To Promote Diversity in Health-Related Research

This NIH-wide program provides supplemental support to existing NIH-funded institutions to encourage the participation of individuals from groups currently underrepresented in biomedical, clinical, behavioral, and social sciences throughout the continuum from high school to the faculty level. There is some evidence that individuals who have participated in the NIH administrative supplement program preferentially conduct research in areas related to minority health or health disparities.

National Institute on Minority Health and Health Disparities Extramural Loan Repayment Program for Health Disparities Research

The Loan Repayment Program for Health Disparities Research (LRP–HDR) recruits, trains, and retains highly qualified health professionals through repayment of educational loans in exchange for conducting minority health or health disparities research. More than 60 percent of LRP–HDR scholars are from racial/ethnic minority populations. Since its inception, more than 2,200 awards to individuals representing multiple disciplines including internal medicine, mental health, behavioral science, anthropology, pharmacology, cardiology, epidemiology, health sciences, oncology, psychology, and gastroenterology have been made through this program.

Question. Does the Research Center in Minority Institutions (RCMI) plan to dedicate funding that would further enhance research infrastructure and training opportunities at RCMI institutions that have been dedicated to addressing these concerns? Also, given the importance of science networking within minority serving institutions, are there plans for the RCMI Clinical Translational Research program

to work with the RCMI Translational Research Network to promote more multi-site clinical trials to address health disparities in minority/underserved communities?

Answer. An environment that is conducive to health-related research at academic institutions, including minority institutions, is a priority for the NIH. The NIMHD RCMI program supports the basic underpinning of research to further, biomedical, clinical, behavioral, and social sciences research activities. Enhancement of infrastructure and research capacity includes renovation/alteration of new research facilities, creating shared resources that result in economies of scale for research projects, and developing a diverse scientific workforce. This investment has been instrumental in the engagement of racial/ethnic minority populations in research and in the translation of research advances into culturally competent, measurable, and sustained improvements in health outcomes.

The RCMI Infrastructure for Clinical and Translational Research (RCTR) awards support the development of infrastructure required to conduct clinical and translational science in RCMI institutions. This infrastructure enhancement may include outpatient clinical research resources, biostatistical support, core laboratories, or facilities to support patient-oriented investigations such as community-based research. Multi-site investigations on those diseases that disproportionately impact health disparity populations are an integral component of the RCTR program. As the Data and Technology Coordinating Center for RCMI, the RCMI Translational Research Network will continue working with RCTR to promote scientifically sound, clinical trials involving multiple academic institutions, clinical sites, and community health providers.

QUESTIONS SUBMITTED BY SENATOR HERB KOHL

NATIONAL CHILDREN'S STUDY

Question. The National Institutes of Health (NIH) has announced a change in the National Children's Study (NCS) Vanguard contracts from academic centers to a national research firm. How do these changes in contracts affect the scientific integrity of the study?

Answer. The change in Vanguard Study operations, to have primary data collection performed by another contractor, affects 7 of the 40 Vanguard locations for a period of 6 months, from July to December 2012. That contractor, Research Triangle Institute, was selected through a full and open competition in 2010 for the purpose of providing additional data collection capacity for the Vanguard Study. During this 6-month period, the seven locations will participate in a pilot project to optimize the transition process and maintain the scientific quality and integrity of the Study.

Prior to July 2012, new funding opportunities to provide data collection for all of the Vanguard locations will be announced. These new contracts will also be awarded through a full and open competition. All current contractors are eligible to compete for these new contracts. Following award of those contracts, all Vanguard Study centers, including the seven locations in the transition pilot, will transition to the new contractors.

Question. What is NIH's plan for transitioning from a decentralized, academic center based recruitment strategy to a recruitment strategy with a centralized, national research firm?

Answer. The NIH is currently planning recruitment for the NCS Main Study, which is a separate activity from the Vanguard Study. Based on data from the Vanguard Study and consultation with the NCS Federal Advisory Committee and other experts, primary recruitment for the Main Study will be conducted through healthcare providers. We are currently asking for input and gathering additional data on implementation of a healthcare provider approach. New solicitations for recruitment and data collection for the Main Study will be made through a full and open competition. We anticipate that multiple contracts will be awarded. We also intend to award new contracts for supplemental recruitment to target populations that, on the basis of demographics or potential environmental exposures, may be under-represented if one used only a provider based approach.

Question. What is NIH's plan, if any, to collaborate with the current Vanguard centers to maintain those children who have already enrolled in the studies? What are the logistical challenges to this transition?

Answer. Current NCS Vanguard Study contracts expire over the next 17 months; new contracts will be awarded following full and open competitions. The NCS is working with current contractors to ensure the orderly transition of data collection services and of relationships with participants, communities, and other local institutions. As is usual with longitudinal studies that extend across many years, indi-

vidual contractors may continue to change during the course of the study, and it is important for the NCS to have procedures in place to ensure smooth transitions that may occur in the future.

The Vanguard Study will continue to pilot study methods in its current 40 locations, several years in advance of the Main Study, following the children already recruited by the Vanguard Study until they turn 21. In this follow-up phase, it will use a smaller number of contractors than in its earlier recruitment phase, thus following recommendations in the Institute of Medicine report from 2008 and realizing cost savings, while improving scientific quality by achieving greater consistency in data and specimen collection among study sites.

Question. What, if any, role will the current Vanguard sites have within the NCS after the NIH ends their contracts?

Answer. The Vanguard Study will continue in the same sites for the next two decades, although it may not be carried out by the same contractors. All Requests for Proposals for both the Vanguard and Main Studies will have full and open competitions. All current contractors can offer proposals for new contracts and also have other options to participate in the NCS, including partnering with a primary data collector, conducting ancillary studies using NCS infrastructure, and doing their own research analyses using NCS data as they become available.

QUESTIONS SUBMITTED BY SENATOR MARY L. LANDRIEU

NATIONAL INSTITUTES OF HEALTH INSTITUTIONAL DEVELOPMENT AWARD PROGRAM

Question. The National Center for Research Resources (NCRR), an Institute within the National Institutes of Health (NIH), houses a program called the Institutional Development Award (IDeA program). The IDeA program funds research in States that are traditionally underrepresented within the NIH, including Louisiana.

In the fiscal year 2012 U.S. Department of Health and Human Services budget, the Congress increased the funding for the IDeA program by $46 million. However, for the fiscal year 2013 budget year, the President proposes a $48 million decrease. It appears that this money is being taken away in order to help fund the new National Center for Advancing Translational Sciences (NCATS).

At a time when NIH budgets are flat, and when the most heavily funded States will continue to be funded as they always have, why would the administration propose reducing the one pot of money that is specifically designed for States that have traditionally been underfunded?

Answer. For fiscal year 2012, the IDeA program was provided with a 21-percent increase in the congressional appropriation, or approximately $50 million, in funding over fiscal year 2011, while most other NIH programs were held relatively flat. For fiscal year 2013, the budget proposes $225 million for the IDeA program, about the same as the fiscal year 2011 level, and approximately $50 million below fiscal year 2012. The IDeA program is valued by NIH and gives many investigators at less research-intensive institutions an opportunity to contribute to biomedical research. Within a constrained budget environment, NIH believes that the IDeA program should not be treated differently than most other programs in the fiscal year 2013 NIH budget which are flat with fiscal year 2011. With regard to NCATS, the fiscal year 2013 budget requests an increase because of the need for innovative solutions to the bottlenecks currently in the development pipeline that hinder the movement of basic research findings into new diagnostics and therapeutics for patients. The request for IDeA is made in the context of the total NIH budget and not as a particular offset to any one program or line item.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES FUNDING LEVELS

Question. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to conduct and support innovative diabetes research that will move the Nation forward in treatment, enhanced detection, and prevention of diabetes.

In the proposed fiscal year 2013 HHS budget, the NIDDK received a slight decrease in funding of $2 million compared with the fiscal year 2012 funding level. I am concerned that this decrease in funding will affect NIDDK's ability to continue to make progress on promising diabetes research.

Would you please share with us the percentage of grants that NIDDK has been able to fund over the past 2 years and how this cut will affect grants/research going forward?

Answer. In fiscal year 2010 and fiscal year 2011, the success rates for NIDDK-funded Research Project Grants (RPGs) were 26 percent and 21 percent, respectively; the estimate for fiscal year 2012 is 20 percent. In the fiscal year 2013 President's budget request, there is an overall reduction of 1 percent in the average cost of both competing and noncompeting RPGs. NIDDK also expects to have fewer noncompeting grants that require funding in fiscal year 2013. As a result, the number of new or competing RPGs would increase by 43, resulting in an estimated success rate of 21 percent in fiscal year 2013. The slight net decrease in funding of $2.798 million, or −0.1 percent, in the President's budget request, compared with the fiscal year 2012 funding level, is due primarily to a reduction in NIDDK HIV/AIDS research that results from $30.951 to $27.635 million or $3.316 million in AIDS research. The AIDS reduction is a result of the annual AIDS priority level review of all expiring grants in fiscal year 2012 that would be competitively submitted for funding in fiscal year 2013. These projects are no longer considered to be aligned with the fiscal year 2013 priorities for trans-NIH AIDS research. The overall non-AIDS total is increased by $518,000 resulting from the increased funding in R&D Contracts and National Research Service Award Research Training. The AIDS reduction plus a non-AIDS increase results in a $2.798 million reduction in the total NIDDK.

GESTATIONAL DIABETES

Question. Currently, gestational diabetes is a disease affecting up to 18 percent of all pregnant women. Long-term health consequences face women and children who have gestational diabetes, such as susceptibility to type 2 diabetes.

Would you please provide a list of the specific research initiatives or projects NIDDK or other Institutes at NIH are currently funding to address this issue?

Answer. The NIDDK and National Institute of Child Health and Human Development are vigorously supporting research and other efforts to address gestational diabetes mellitus (GDM) and its immediate and long-term health consequences for women and their children. While complete data for fiscal year 2012 are not yet available, we are pleased to provide examples of a number of current efforts. The NIDDK, under its "Healthy Pregnancy Program," is supporting three major GDM-related initiatives:

—A multi-center research consortium testing interventions in diverse groups of overweight and obese pregnant women to improve weight and metabolic outcomes in both the women and their offspring. This effort is co-supported by NICHD, National Heart, Lung, and Blood Institute (NHLBI), and the NIH Office of Research on Women's Health.

—The Hyperglycemia and Adverse Pregnancy Outcomes Follow-up Study, which will examine whether elevated blood sugar levels less severe than GDM carry similar long-term health risks for women and their offspring.

—An educational component, led by the National Diabetes Education Program (NDEP), that targets women with a history of GDM, their families, and their healthcare providers to raise awareness of health risks and the steps that women and their children can take to avert health problems. The NDEP is a joint program of the NIDDK and the Centers for Disease Control and Prevention (CDC).

NIDDK and NICHD also support basic and clinical research to better understand GDM, as well as to identify ways to prevent or treat it and its long-term health risks. For example, several studies focus on understanding how maternal diet and metabolism affect fetal development and incur long-term risks for obesity and other health problems. Researchers are also continuing to study women at risk for type 2 diabetes due to GDM history who participated in NIH's landmark Diabetes Prevention Program clinical trial. Researchers are also:

—following a large population of women with a history of GDM to understand how the frequency and duration of their breastfeeding may prevent their later development of type 2 diabetes;

—screening women for GDM in the first months of pregnancy, to understand whether early-emerging and later-emerging forms of GDM differentially affect maternal and child outcomes. Other goals of the research are to refine GDM tests and to determine, at a systems level, whether routine screening for early GDM in obese women improves outcomes in the women and their children;

—searching for abnormalities in fetal development of heart function and other factors that could eventually cause adult heart disease in offspring of pregnant laboratory animals with GDM; and

—analyzing post-partum maternal and infant cord blood samples to determine whether specialized types of human fat and immune cells could be novel biochemical markers to help predict future GDM.

NATIONAL CANCER INSTITUTE FUNDING LEVEL

Question. The funding for NIH, and in turn, National Cancer Institute (NCI), has eroded since fiscal year 2010, not only due to lost purchasing power as a result of biomedical inflation but also due to outright cuts in fiscal year 2011.

How has the eroded funding affected the Institute in terms of the number of new grants funded and harm to existing grants? What decisions have you had to make as a result? If we could restore funding to fiscal year 2010 levels, or even better, increase funding above those levels, what could you do with the new money?

Answer. As a result of the decrease to the NCI budget in fiscal year 2011, we funded 1,106 competing grants, 147 fewer than in 2010. For the 3,769 existing grants that received continuation funding in 2011, the amount was reduced by 3 percent from the fiscal year 2010 level. Principal investigators could have used a number of strategies to accommodate lower funding levels, including reducing staff, deferring the purchase of equipment or supplies, or scaling back their projects in some way.

In fiscal year 2011, NCI applied reductions of 2 to 5 percent in most budgets for our many activities—including the intramural programs, contracts at NCI-Frederick and elsewhere, the NCI-designated cancer centers, and the operating budgets of all NCI components. NCI's leadership made choices to achieve the necessary savings while preserving core elements needed to sustain the pace of discovery. NCI leadership has carefully assessed the overall research portfolio and determined the areas where, in our professional judgment, increased funding could have additional impact over time in reducing cancer incidence and mortality. Any increase in funding would be used in part to increase support for new research grants, especially grants to new investigators to support new ideas. Other critical areas that could receive additional support include cancer genomics and transformation of NCI's clinical trials to increase efficiency and reflect the state of the science. An increase to our appropriation could also allow NCI to fund additional grants through the new Provocative Questions project by augmenting the $15 million that was dedicated to the project. Additional resources could support more research toward solving some of the enduring paradoxes in cancer research.

NATIONAL CANCER INSTITUTE—DRUG RESISTANCE

Question. We've heard reports of some targeted treatments achieving incredible results, but then cancers stop responding to those drugs. What is the NCI doing to understand and overcome this drug resistance?

Answer. One of the most disappointing features of the development of new targeted therapeutics is how routinely drug resistance emerges and the disease begins to progress. Resistance to treatment with anticancer drugs results from a number of factors—every cancer expresses a different array of drug-resistance genes, and various mechanisms have evolved as protection from toxic agents. As therapy has become more effective, acquired resistance has become common. NCI is aggressively pursuing research to gain an understanding of the mechanisms that lead to drug resistance and is looking for agents that overcome these mechanisms. NCI is supporting studies of combination therapies for patients whose disease has become resistant to therapy, as well as exploring alternative approaches through the Provocative Questions Initiative to determine if controlling rather than killing cancer cells can avoid the development of drug resistance.

One example of the development of resistance following dramatic response is the clinical experience with the targeted drug vemurafenib (Zelboraf), a BRAF inhibitor that has been shown to nearly double the survival of patients with advanced melanoma. Because nearly one-half of all cases of metastatic melanoma—about 4,000 patients per year—have the BRAF mutation, vemurafenib represents a significant breakthrough in treatment. Unfortunately, after an average of 8 months of treatment, many patients become resistant to the drug and their disease begins to progress. However, with NCI support, researchers are making headway in understanding vemurafenib resistance. Recent data from Memorial Sloan Kettering, for example, demonstrated that some resistant BRAF-mutated melanoma cells produce a shortened version of the mutated BRAF protein that remains active even in the presence of vemurafenib. Strategies to overcome the resistance include finding ways to increase potency of the therapy, disrupting the activity of the altered form, or combining therapies. Other leads have come from researchers at the Moffitt Cancer Center, who identified a new approach utilizing a small molecule inhibitor called

XL–888 to target a family of proteins known as Heat Shock Proteins 90 (Hsp90). The Moffitt researchers reported preclinical data that XL–888 overcame six different models of vemurafenib resistance, demonstrating its therapeutic potential. This work was made possible by early NCI research on Hsp90 as an anticancer agent.

Melanoma is just one example of a disease in which drug resistance is driving creative approaches in cancer research. The drug imatinib (Gleevec), for example, is widely recognized for its success in treating chronic myeloid leukemia by targeting a protein known as BCR–ABL. However, some CML patients relapse when new mutations make the BCR–ABL protein resistant to Gleevec, preventing it from binding to its target and allowing the abnormal enzyme to drive white blood cell growth, again despite treatment. It is encouraging to report that NCI-supported research has identified a number of drugs that can target BCR–ABL proteins even after they acquire mutations that confer resistance to Gleevec. Although two of these, approved a few years ago, could not overcome a relatively common resistance mutation, a third generation of drugs has a new way to attack the mutation, freezing the target protein and rendering it inactive. This example illustrates another important point: many different research fields—from genetics to structural biology to pharmacology—were required for these advances in treatment. The need for multidisciplinary teams to address key questions like drug resistance in cancers increasingly defines modern biomedical research.

NATIONAL CHILDREN'S STUDY

Question. NIH wants to cut 15 percent from National Children's Study's (NCS) current $193 million budget in fiscal year 2013 by shifting away from the sampling plan put forth by the Institute of Medicine in 2008 to an health maintenance organization (HMO)-based sample.

New Orleans was selected as one of the sites for national sampling and this is particularly important because, as Louisiana is near the bottom of every health outcome ranking and near the top in indicators of poverty, this new knowledge could prove invaluable to improving both. The gulf region has a number of health disparity issues and a large number of uninsured mothers who do not participate in an HMO.

How do you plan on maintaining the scientific integrity of the NCS study so that it reflects a national sample, including unique populations such as those in the gulf region?

Answer. The change in the NCS Study design is being considered primarily for scientific reasons but also with awareness of our need to be fiscally responsible. It is based on data generated during the ongoing Vanguard, or pilot phase, of the NCS. As currently envisioned, the NCS Main Study would use a provider-based participant selection and recruitment strategy that the NIH and the Agency for Healthcare Research and Quality have both employed effectively in other studies. This approach uses research-ready healthcare provider networks as the primary source for recruitment. The NCS would gain additional participants through the award of contracts for supplemental recruitment from secondary sources (such as title V clinics, Indian Health Service clinics, or contract research organizations) to assure inclusion of appropriate population groups, specifically those with health disparities. The use of these two coordinated selection and recruitment strategies would improve the quality of the Main Study and allow analyses not feasible with either approach alone.

If adopted, this revised approach would offer several advantages, including:

—greater recruitment efficiency;

—leveraging access to consenting participants' electronic health records, thus improving the amount and consistency of data collected while lowering costs;

—the potential to leverage the existing infrastructure of networks of healthcare providers, again improving the quality of data and lowering costs;

—allowing built-in continuity for participants who move but remain within the provider network (many provider networks have statewide or regional coverage) or join another provider network affiliated with the Main Study.

Current Vanguard Study contracts are due to expire over the next 17 months. New contracts are required to continue into the next phase of the Vanguard Study, and the NCS has issued a pre-solicitation to request preliminary information on the services available to meet the study's evolving needs. (Please see https://www.fbo.gov/index?s=opportunity&mode=form&id=674a4f3a690d6584870fc84c9cb2b511&tab=core&-cview=0.) All new Requests for Proposals for both the NCS Vanguard and Main Studies will have full and open competitions. Whoever is awarded the new contracts, the NCS plans to remain in the Vanguard locations and to following current Vanguard participants until the last enrolled child turns 21 years old.

Question. On a related topic, Tulane University, in New Orleans, was one of the sites selected for national sampling. The New Orleans Study Location represents a strong collaboration among major healthcare providers and universities, including Tulane, LSU, and Ochsner, and employs many full-time and part-time professionals.

Termination of the contract would be a very significant loss both to the universities, the local community and damage the capacity that has been built.

How will this new system account for the loss of expertise and jobs at study sites throughout the Nation?

Answer. To date, the NCS Vanguard Study has accomplished what it set out to do, provide data on recruitment and early retention into the Study. We will continue to follow all children born into the Vanguard Study, until age 21. We have no intention to lose NCS participants from the Vanguard Study; instead, we are developing and field testing a proactive plan that includes personal contacts, special events for participants, linkages to local health resources through other Health and Human Services programs, returning results of Study assessments, and soliciting feedback about the Study experience. In addition, participants that might have been lost under the original Study design because they moved out of a particular geographic area might still be included in a health provider network involved in the Study.

Current NCS Vanguard Study contracts expire over the next 17 months, but none are expected to be prematurely terminated. The NCS is working to standardize the transition process so that if a new contractor replaces a current contractor at an NCS location, the data, the knowledge, the relationships and the continuity can be maintained. We are targeting a minimum 90-day overlap in contracts, to allow for an orderly and systematic transfer.

All new Requests for Proposals for both the Vanguard and Main Studies will have full and open competitions. Academic institutions can offer proposals for new Study contracts for primary data collection, and have other options as well, including partnering with a primary data collector, conducting ancillary studies using NCS infrastructure, or doing their own research analyses using NCS data as they become available. Finally, contractors that complied with NCS specifications for field operations will have established a platform that is flexible and adaptable to multiple uses, so they can leverage that investment for additional projects.

NATIONAL INSTITUTES OF HEALTH INVESTIGATOR-INITIATED RESEARCH

Question. Will the investigator-initiated research be able to grow in the area of translational science, and will basic science be a part of it?

Answer. Within the administration's fiscal year 2013 budget request for NIH of $30.86 billion, the same overall program level as in fiscal year 2012, we plan to continue to maintain funding emphasis and increase the overall number of Research Project Grants (RPGs). RPGs are NIH's fundamental funding mechanism for investigator-initiated research. The NIH budget request will support an estimated 9,415 new and competing RPGs in fiscal year 2013, an increase of 672 more than fiscal year 2012. The total number of RPGs funded for fiscal year 2013 is expected to be around 35,888, or approximately the same as the 35,944 estimated for fiscal year 2012.

In pursuit of its mission to alleviate the burden of illness, NIH supports a continuum of research, from understanding basic causes and mechanisms of health and disease to translating that understanding into new ways of identifying and intervening upon disease processes, and in turn translating those new interventions into clinical practice. As the leading supporter of basic biomedical research in the world, NIH commits slightly more than one-half its annual budget to better understand the basics of how life works.

Yet, the path from basic research to clinical practice is not always linear; each step in the process may inform any other step. For example, clinical research can inform basic research. This is exemplified by a recent clinical finding made by NIH scientists in the intramural program's Undiagnosed Diseases Program that has led to a dramatic new understanding of basic functioning. These scientists studied a pair of sisters from Kentucky who suffered from joint pain and a mysterious calcification of the arteries in their extremities. Their research uncovered a novel genetic condition that affected a previously unknown enzyme pathway, resulting in blocked arteries. The discovery provides a dramatically new understanding of how large arteries maintain normal functioning, and it has opened the door to many other lines of inquiry across both basic and clinical arenas.

The proposed increase in RPGs provides the framework for NIH to prospectively expand investigator-initiated research across the continuum of biomedical and behavioral science. Each new finding in one arena will inform and lead to new investigations in other areas of basic, translational, and clinical research.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

CONGENITAL HEART DISEASE

Question. Congenital Heart Disease (CHD) is one of the most prevalent birth defects in the United States and a leading cause of birth defect-associated infant mortality. Due to medical advancements more individuals with congenital heart defects are living into adulthood. Please provide an update of research within National Institutes of Health (NIH), particularly the National Heart, Lung, and Blood Institute (NHLBI) related to congenital heart defects across the life-span.

The healthcare reform law included a provision, which I authored, that authorizes the Centers for Disease Control and Prevention (CDC) to expand surveillance and track the epidemiology of CHD across the life-course, with an emphasis on adults. The Consolidated Appropriations Act of 2012 provided the CDC with $2 million in new funding for enhanced CHD surveillance. Please describe how NIH is working with CDC to enhance CHD surveillance across the life-course. CDC is using a portion of the newly appropriated funds to convene a congenital heart defects experts meeting. Please summarize NIH's role at the expert meeting and in shaping the meeting's research agenda.

Answer. NHLBI continues to make an extensive investment in research related to congenital heart defects across the life-span. The Institute is working in conjunction with the CDC on a number of activities to expand surveillance of CHD and improve our understanding of its epidemiology, including the following:

Newborn Screening for Critical Congenital Heart Diseases.—In September 2011, Secretary Sebelius recommended that screening for Critical Congenital Heart Diseases (CCHD) be added to routine newborn screening and called for research to address evidence gaps that are presently constraining implementation of screening programs. In response, the NHLBI, the National Institute of Child Health and Human Development (NICHD), the CDC, and other Federal partners involved in newborn screening have set up regular calls and meetings to determine how best to proceed. As an example, the CDC and NHLBI have been discussing details of a common nomenclature to be used in screening for cardiovascular malformations and the potential for combining the efforts of the CDC's robust birth defects case-ascertainment and research programs with the NHLBI-funded Pediatric Heart Network and the Pediatric Cardiac Genomics Program to answer research questions about approaches to and effectiveness of screening for CCHD.

Data Set on Sudden Cardiac Death in the Young.—Development of effective screening and prevention strategies for Sudden Cardiac Death in the Young (SCDY) is limited by a lack of prospectively defined epidemiological data, including incidence rates and etiology. NHLBI is planning an innovative program to address this knowledge gap. Its initial phase, in coordination with the CDC and others, would be to develop a surveillance system and registry that broadens and enhances the activities of the National Center for Child Death Review and the Sudden Unexpected Infant Death Registry. This phase would result in the first prospective, population-based U.S. data set on SCDY; it would include data from death certificates, medical records, death-scene investigations, and pathology reports and also include serum samples for DNA extraction. It would be followed by a second phase that would support scientific research using the data set.

Congenital Heart Public Health Consortium.—NHLBI and the CDC were founding Federal advisors to the Congenital Heart Public Health Consortium (CHPHC), a group formed in 2008 to address the public health burden of CHD. The CHPHC has united a variety of organizations, including Federal agencies, patient advocacy groups, and physician associations that have a strong interest in CHD. Its approach includes strong emphasis on enhanced surveillance via monitoring CHD throughout the lifespan, as well as assessment of the needs of patients and families for chronic disease management and age-appropriate preventive care. Representatives from NHLBI and the CDC currently serve as advisors to the Consortium Steering Committee.

NHLBI is working closely with the CDC to organize the upcoming congenital heart defects experts meeting which will occur September 10–11, 2012. Its goal is to determine priorities for public health research on congenital heart disease across the life course in the United States. The planning committee consists of representatives from the CDC and the NHLBI and pediatric cardiologists from academia. The meeting agenda will focus on three main areas of public health concern for congenital heart disease—epidemiology, long-term health outcomes (both medical and nonmedical), and health services research (including access to care, employability,

and economics). Invitations have been sent to a variety of experts, including pediatric cardiologists, adult congenital heart specialists, adult cardiologists with expertise in epidemiology, epidemiologists, cardiac surgeons, health services/outcomes researchers, patient advocates, health economists, and other Federal partners.

ANTIMICROBIAL RESISTANCE

Question. NIH is part of an Interagency Task Force on Antimicrobial Resistance (ITFAR) that was created in 1999. What is the status of the subcommittee's recommendations to address the complex issue of antimicrobial resistance?

Answer. In 2001, the ITFAR published a Public Health Action Plan to Combat Antimicrobial Resistance (the Public Health Action Plan). This plan was updated, with stakeholder input, in 2011 and lays out specific action items in the areas of Surveillance, Prevention and Control, Research, and Product Development to address the complex issue of antimicrobial resistance. The updated plan is posted here: http://www.cdc.gov/drugresistance/pdf/public-health-action-plan-combat-antimicrobial-resistance.pdf.

Progress toward the implementation of Action Items under each of the goals in the Public Health Action Plan is reported annually by all participating agencies and documented at this link: http://www.cdc.gov/drugresistance/annualReports.html.

At NIH the National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute responsible for research on antimicrobial resistance. NIAID supports basic, translational, and clinical research to understand and combat the problem of antimicrobial resistance. NIH, with support from NIAID, co-chairs the ITFAR and conducts research addressing several of the goals of the Public Health Action Plan, including goals supporting basic, applied, and clinical research on antimicrobial resistance. For example, NIAID is supporting a robust response to Action Items under Goal 7.2: Design and implement studies focused on optimizing the dose and duration of antibacterial agents prescribed for treatment of community-acquired pneumonia, urinary tract infections, skin and soft-tissue infections, and other infectious illnesses. To address this goal, NIAID is supporting clinical trials to inform the rational use of existing antimicrobial drugs to help limit the development of antimicrobial resistance, and is also supporting a clinical study to optimize the use of colistin, an antibiotic approved in the late 1950s that is increasingly being used today to treat multi-drug resistant Gram-negative infections. NIAID-supported clinical trials evaluating the effectiveness of different drug combinations in treating influenza, HIV, and malaria are also ongoing.

In addition, NIAID supports basic research to identify new antimicrobial targets and translational research on strategies to combat antimicrobial-resistant infections. NIAID supports the development of effective diagnostics, drugs, and vaccines to identify, treat, and prevent infectious diseases. As part of this effort, NIAID provides a broad array of preclinical and clinical research resources to researchers in academia and industry designed to facilitate the movement of a product from bench to bedside. By providing these critical services to the research community, NIAID can help to bridge gaps in the product development pipeline and lower the financial risks incurred by industry to develop novel antimicrobials. For example, NIAID supports the preclinical development of new antibacterial agents through directed contracts to companies involved in novel drug design and synthesis. These contracts were solicited through a Broad Agency Announcement entitled "Development of Therapeutics for BioDefense." To foster clinical research on antimicrobial resistance, in January 2012, NIAID released a request for applications to support a new leadership group for an antibacterial resistance clinical trial network similar to the existing HIV/AIDS clinical research networks (http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-12-019.html). The antibacterial resistance leadership group would develop and implement a comprehensive clinical research agenda to address the pressing problem of antibacterial resistance.

The research described above represents only a small portion of NIAID's significant investment in research addressing the problem of antimicrobial resistance. For more information, please visit the ITFAR annual report linked above as well as the NIAID Web page at: http://www.niaid.nih.gov/topics/antimicrobialresistance/Pages/default.aspx.

DIABETES PREVENTION PROGRAM

Question. Diabetes Prevention Program (DPP) was a clinical research study investigating the impact of lifestyle and drug interventions on diabetes prevention. Two new NIH initiatives have taken advantage of DDP's findings and are building on the discoveries. Please summarize the two new programs and explain how they are different from DPP.

Answer. NIH's landmark DPP clinical trial proved that an intensive lifestyle intervention reduced rates of diabetes incidence by 58 percent among an at-risk population. The lifestyle intervention was effective in all ethnic groups, and was particularly effective in those older than age 60 at the beginning of the trial, among whom it reduced diabetes incidence by 71 percent. The trial also found that the safe, well-tolerated, inexpensive, generic diabetes drug metformin reduced diabetes incidence by 31 percent, and was most effective in younger participants, and women with a history of gestational diabetes, who otherwise develop type 2 diabetes at particularly high rates.

NIH has built on these major findings in several ways. First, most of the DPP participants elected to enroll in a follow-on study, the DPP Outcomes Study (DPPOS). Phase 1 of this study showed that both interventions are durable, and continue to provide significant diabetes prevention benefit for at least a decade. Moreover, participants in the lifestyle arm of the study had dramatically better quality of life and a reduced need for medications to control blood pressure and cholesterol. Both lifestyle and metformin were also found to be highly cost effective, and metformin was actually found to be cost saving. Phase 2 of DPPOS will assess the long-term impact of the interventions on diabetes complications. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is also currently working with National Cancer Institute (NCI) to determine the feasibility of detecting potential effects of the interventions on later development of cancer.

To develop ways to make diabetes prevention more practical and affordable, the NIH-funded research to translate the DPP lifestyle intervention into widespread practice. Some particularly promising projects have focused on research to reduce costs, while maintaining efficacy, by delivering the intervention in a group-based form. Strong preliminary results from one such ongoing study led to creation of the "National" DPP (NDPP) by the Centers for Disease Control and Prevention, which is working to train and credential a cadre of group lifestyle intervention providers for diabetes prevention. Many of the providers trained so far work at YMCAs, which now provide access to these services to people with prediabetes at more than 50 locations (http://www.ymca.net/diabetes-prevention/participating-ys.html). Additional work to help realize the potential of the DPP and other diabetes studies is being conducted through the Diabetes Translational Research Centers program.

Detailed DPP genetic analyses have shown that the lifestyle intervention helps prevent diabetes even among those at greatest genetic risk. Interestingly, a gene was identified that substantially reduces the efficacy of metformin in about 1 in 3 people. NIH is supporting a June 7 conference on metformin pharmacogenetics to explore this and related issues.

Question. Although the long-term outlook for children with type 1 diabetes has improved, the rates of diagnoses continue to rise. Please provide an update on research efforts within NIH related to type I diabetes and how additional innovations in research could prevent children from developing this disease.

Answer. NIH-supported research has shown that people with type 1 diabetes are living longer and healthier lives than ever before. However, research has also shown that rates of type 1 diabetes are rising, especially in children under 4 years of age. One approach to curb the rising rates of type 1 diabetes is to identify a disease prevention strategy. Toward this goal, the NIDDK has undertaken a bold, long-term initiative—called The Environmental Determinants of Diabetes in the Young (TEDDY) study—to identify the environmental triggers that intersect with genetic risk and lead to the development of type 1 diabetes. More than 8,600 newborns are enrolled in the study—after screening more than 420,000 newborns—and researchers are collecting biological samples, as well as information about the children's diet, illnesses, vaccinations, and allergies, until the children are 15 years of age. Knowledge gained from the TEDDY study can revolutionize our ability to prevent type 1 diabetes. For example, the discovery of a viral cause could lead to development of a vaccine to prevent the disease. Identification of a dietary factor as a cause could lead to changes in feeding practices.

NIH-supported researchers are also conducting clinical trials testing promising prevention therapies in people at high genetic risk of developing type 1 diabetes. For example, the NIDDK's Type 1 Diabetes TrialNet is conducting two clinical trials testing agents to prevent the disease in relatives of people with type 1 diabetes. The NICHD's Trial to Reduce IDDM (insulin-dependent diabetes mellitus) in the Genetically At-Risk, or TRIGR, is testing whether hydrolyzed infant formula compared to cow's milk-based formula decreases the risk of developing type 1 diabetes in at-risk children.

NATIONAL CHILDREN'S STUDY

Question. The National Children's Study (NCS) will examine environmental influences on the health and development of a cohort of U.S. children from birth until age 21. Field work for the study ended in March 2012, which provided data about recruitment processes and costs associated with the study. How are these data being used to inform the cost-effectiveness of the main study?

Answer. Data generated during the ongoing Vanguard, or pilot, phase of the NCS showed that a study design based on recruiting through healthcare providers was more efficient than recruitment through door-to-door contact or direct outreach to the public. Other large Federal studies have also effectively employed provider-based approaches.

More specifically, the NCS uses several methods to analyze costs and cost effectiveness. We maintain our own internal data base of contract invoices and analyze the invoice data for costs and level of effort based on activity. In addition, operational data elements that record the activities, logistics and costs of all aspects of the Vanguard Study have been embedded into the protocol data collection. These operational data elements are the primary outcome measures for the Vanguard Study goals of testing feasibility, acceptability, and cost-of-study operations. These data are captured in a central data repository and analyzed every 2 weeks to guide operations and assess overall data quality. In a third approach, two contractors, one a consulting firm and the other an academic institution, have been engaged to project operational resources and potential costs based on data from the field.

Question. A recent restructuring of the field operations will centralize some data collection to a single subcontractor. Please explain the rationale and cost-effectiveness of this restructuring.

Answer. The change in Vanguard Study operations, to have primary data collection performed by another contractor, affects 7 of the 40 Vanguard locations for a period of 6 months, from July to December 2012. That contractor, Research Triangle Institute, was selected through a full and open competition in 2010 for the purpose of providing additional data collection capacity for the Vanguard Study. During this 6-month period, the seven locations will participate in a pilot project to optimize the transition process and maintain the scientific quality and integrity of the Study.

Prior to July 2012, new funding opportunities to provide data collection for all of the Vanguard locations will be announced. These new contracts will also be awarded through a full and open competition. All current contractors are eligible to compete for these new contracts. Following award of those contracts, all Vanguard Study centers, including the seven locations in the transition pilot, will transition to the new contractors.

Question. The NIH/NICHD has suggested an alternative sampling strategy that uses health plans or health providers to identify and recruit pregnant women. How can the proposed strategy ensure the sample represents all U.S. children, particularly uninsured, minority, immigrants, and low-income children?

Answer. As currently envisioned, the NCS Main Study would use a provider-based participant selection and recruitment strategy that the NIH and the Agency for Healthcare Research and Quality have both employed effectively in other studies. This approach uses research ready healthcare provider networks as the primary source for recruitment. The NCS would gain additional participants through the award of contracts for supplemental recruitment from secondary sources (such as title V clinics, Indian Health Service clinics, or contract research organizations) to assure inclusion of appropriate population groups, specifically those with health disparities. The use of these two coordinated selection and recruitment strategies would improve the quality of the Main Study and allow analyses not feasible with either approach alone.

QUESTIONS SUBMITTED BY SENATOR JACK REED

NATIONAL CHILDREN'S STUDY

Question. You mentioned during the hearing that the proposed re-design of the National Children's Study (NCS) will be as effective and more efficient in enrolling study participants. However, you didn't mention the scientific basis for this re-design. Did you consult the national panel of experts—the Institute of Medicine (IOM), and the National Children's Study Federal Advisory Committee that informed the original design of the study with this new re-design? If these individuals and entities have already been consulted, do you plan to make those comments available to the public? If they have not already been consulted, do you intend to consult these groups and make those comments public?

Answer. The change in NCS design is being considered primarily for scientific reasons but also with awareness of our need to be fiscally responsible. It is based on data generated during the ongoing Vanguard, or pilot phase, of the NCS. The Vanguard data showed that the proposed study design would not enroll sufficient numbers of families within a scientifically acceptable timeframe or within a fiscally sound budget. Pilot testing conducted through the Vanguard sites showed that a study design based primarily on recruiting participants through healthcare providers was most efficient and could offer scientific advantages that would more than offset its scientific compromises. This provider-based approach also has been employed effectively in other large Federal studies. The President's fiscal year 2013 budget request, which shows a reduction of approximately 15 percent, to $165 million annually, for the NCS, appropriately reflects these proposed design changes.

As currently envisioned, the NCS Main Study would use a provider-based participant selection and recruitment strategy that the NIH and the Agency for Healthcare Research and Quality have both employed effectively in other studies. This approach uses research ready healthcare provider networks as the primary source for recruitment. The NCS would gain additional participants through the award of contracts for supplemental recruitment from secondary sources (such as title V clinics, Indian Health Service clinics, or contract research organizations) to assure inclusion of appropriate population groups, specifically those with health disparities. The use of these two coordinated selection and recruitment strategies would improve the quality of the Main Study and allow analyses not feasible with either approach alone.

If adopted, this revised approach would offer several advantages, including:

—greater recruitment efficiency;

—leveraging access to consenting participants' electronic health records, thus improving the amount and consistency of data collected while lowering costs;

—the potential to leverage the existing infrastructure of networks of healthcare providers, again improving the quality of data and lowering costs; and

—allowing built-in continuity for participants who move but remain within the provider network (many provider networks have statewide or regional coverage) or join another provider network affiliated with the Main Study.

NCS continues to refer to the IOM report that was written by a panel of experts convened to review the original study design. Many of the changes recommended in the report have already been addressed, including the need for an ongoing Vanguard Study to test the study protocol and scientific methodology. The report also noted that the large number of field contractors was a weakness of the Study design, and the NCS is moving to correct this weakness.

The NCS Study Advisory Committee meets at least four times a year; the April 24, 2012 meeting was the 32d meeting of the subcommittee. These meetings are open to the public, and a public comment period is provided. Presentations to the Advisory Committee also are posted on the NCS Web site. As they have become available, data from the Vanguard Study have been presented at each of the subcommittee's meetings. The topic of a provider-based approach to Study recruitment was discussed twice in the last year with the Advisory Committee, first in April 2011 and then again in July 2011, before being the focus of the entire April 24, 2012 meeting. The NCS Study Director holds weekly national conference calls for Vanguard Study contractors to update them on recent developments and to receive their input. The investigators also provide expertise and comments through a monthly Executive Steering Committee meeting, through 2-day, face-to-face meetings every 6 months, through circulation of all study instruments and protocol changes to all investigators for comment, and through a mailbox account dedicated to contractors.

Question. I am also concerned that the re-design will jeopardize 70 high-quality jobs in Rhode Island, including 20 full-time positions that would have otherwise been created for the Main Study. How will this proposal impact the work of researchers and practitioners already participating in the study and the potential for job growth in my State? Does NIH plan to abandon its commitment to the 105 counties that have been selected to participate in the study?

Answer. To date, the NCS Vanguard Study has accomplished what it set out to do, provide data on recruitment and early retention into the Study. We will continue to follow all children born into the Vanguard Study, until age 21. We have no intention to lose NCS participants from the Vanguard Study; instead, we are developing and field testing a proactive plan that includes personal contacts, special events for participants, linkages to local health resources through other Health and Human Service programs, returning results of Study assessments, and soliciting feedback about the Study experience. In addition, participants that might have been lost under the original Study design because they moved out of a particular geographic area might still be included in a health provider network involved in the Study.

Current NCS Vanguard Study contracts expire over the next 17 months. All Requests for Proposals for both the Vanguard and Main Studies will have full and open competitions. Academic institutions can offer proposals for new Study contracts for primary data collection, and have other options as well, including partnering with a primary data collector, conducting ancillary studies using NCS infrastructure, or doing their own research analyses using NCS data as they become available. Finally, contractors that complied with NCS specifications for field operations will have established a platform that is flexible and adaptable to multiple uses, so they can leverage that investment for additional projects.

As indicated above, the change in study design is based on data generated during the ongoing Vanguard pilot phase of the NCS, which showed that the previously proposed study design would not enroll sufficient numbers of families within a scientifically acceptable timeframe or within a fiscally sound budget. Pilot testing conducted through the Vanguard sites showed that a study design based primarily on recruiting participants through healthcare providers was most efficient and could offer scientific advantages that would more than offset its scientific compromises.

PEDIATRIC CANCER RESEARCH

Question. Dr. Varmus, last year you and Dr. Collins provided me with a detailed explanation of NIH efforts to address pediatric cancers, including late-term effects. However, I am still concerned that a mere 4 percent—just $200 million—of NCI funding is allocated to cancer research specifically for this population. I am concerned that this funding level remains stagnant because the peer-review process doesn't recognize the importance of pediatric cancer research in terms of years of life lost and poor quality of life for many survivors. How could a Pediatric Cancer Study Section improve the funding devoted to pediatric cancer research?

Answer. Over the past year, the National Cancer Institute (NCI) has worked with members of the Congressional Childhood Cancer Caucus to discuss this very question, and to explore how pediatric cancer research proposals fare in comparison to other proposals under the current peer-review process, with a goal of determining whether or not pediatric cancer grant applications are competitive in the peer-review process. NCI performed this analysis, which showed that pediatric cancer grant applications actually have success rates (number of grants awarded/number of grants received) that are equal to—and in some cases higher than—grant applications focusing on adult cancers. NCI further focused on R01 (individual investigator initiated) grant applications to exclude large program grants (such as cancer center support grants, for example) that have little competition. And again the data showed that pediatric cancer-focused R01 grant applications are quite competitive in the peer-review process.

The NIH Center for Scientific Review (CSR), which oversees the NIH peer-review process, considers a number of criteria when it establishes study sections. These criteria were developed by an external blue ribbon panel set up to systematically assess and reorganize CSR's review groups. For example, these guiding principles indicate that applications pertaining to a given disease/organ system are best reviewed in the context of the biological question being addressed. They provide that study section boundaries should not be too broad or too narrow, and that sufficient overlap should exist between other study sections inside and outside their integrated review groups (IRGs—clusters of study sections based on scientific discipline).

Therefore, the NIH has no standing study sections that review applications relevant to specific diseases, groups of diseases, or organ sites; rather, study sections are formed around scientific disciplines, e.g., epidemiology, genomics, therapeutics development, populations, behavior, etc., and are populated by productive investigators with expertise in those areas.

Within the category of pediatric cancer research, applications under consideration for funding pose an extremely diverse set of biological questions, as evidenced by the array of standing study sections that are called upon to review grant applications relevant to pediatric cancer. Because pediatric cancers are so heterogeneous, it makes sense scientifically to distribute review of these applications among multiple study sections.

Data analyzed from fiscal year 2008 through fiscal year 2010 indicate that the NCI supports pediatric cancer research applications via numerous mechanisms, and that support of pediatric cancer research grants has increased during that time period. As previously noted, success rates were in line with—and in many cases exceeded—those for other cancer types. This evidence suggests that pediatric cancer applications are very competitive within NIH's scientific review process.

Additionally, although disease-specific funding estimates can be useful indicators of some focused work, they do not reflect the full level of NCI's investment (approximately $1.9 billion) into research exploring cancer biology and cancer causation—broad areas of inquiry applicable to all types of cancers, including pediatric cancers. It is important to consider NCI's full cancer research portfolio, and to also recognize that investments in one area of cancer research can, and often do, contribute to advances in others. For example, identifying the clinical value of crizotinib in the treatment of adults affected by lung cancer with abnormalities of the Alk gene has led to the current clinical testing children with neuroblastoma whose tumors have Alk abnormalities.

QUESTIONS SUBMITTED BY SENATOR MARK PRYOR

PANCREATIC CANCER RESEARCH

Question. Dr. Varmus, during the hearing you testified that research for pancreatic cancer is being prioritized by National Cancer Institute (NCI) and that the Institute currently has flexibility to fund grant applications that fall below what used to be called the "pay line" in cases where therapeutic progress in relation to a disease has been low. Are there examples you can describe of grants in relations to pancreatic cancer where the Institute exercised this flexibility?

Answer. Pancreatic cancer is a high priority for the NCI, and we are supporting a wide range of research projects to rapidly develop the tools needed to diagnose pancreatic tumors as early as possible, to characterize tumors genetically, and to find new ways to treat this disease. NCI has been paying special attention to grants that might not be funded because they fell below what used to be considered a "payline," a percentile score derived from the results of peer review. Beginning in fiscal year 2011, NCI scientific program leaders have been performing additional evaluations of grant applications to ensure a balanced grant portfolio and to recognize the value of research proposals that are highly original or address important scientific priorities, such as research on pancreatic cancer, even though they might not have received percentile scores that fall within a pre-determined payline. Of the applications that were focused exclusively on pancreatic cancer and were funded in fiscal year 2011, more than one-third were selected as a result of this programmatic review, rather than on the basis of receiving exceptionally high scores.

Examples of pancreatic cancer projects approved by this process include:

—a case-control study aimed at characterizing a select group of biomarker candidates in pancreatic juice that may enable earlier detection;

—a study to develop a multifunctional nanoparticle platform with both imaging and drug delivery capabilities;

—a study of corcetin (a carotenoid molecule isolated from saffron) that has been shown to have anticancer effects as a potential therapy for pancreatic cancer; and

—a study focused on identifying vulnerable areas of pancreatic tumors and overcoming the tough "stromal barrier" of pancreatic tumors that limits the delivery and diffusion of drugs.

LONG-TERM GOALS

Question. In the past, this subcommittee has urged NCI to develop a long-range plan for research in the area of pancreatic cancer research. Research advocates have been disappointed with the plan and view it more as a summary of research that's already underway. Would it be possible for NCI to lay out more of a long-term research strategy—something that sets out concrete goals and objectives for the future that moves beyond current practice?

Answer. Pancreatic cancer is distinct from other cancers due to its complex biology, late manifestation of symptoms, and the lack of early screening tools. In addition, there are a large number of genetic mutations involved, which complicates the development of effective targeted therapies to disable the growth of cancer cells and arrest progression of the disease. These factors explain the poor outcomes for most pancreatic cancer patients. However, there is great opportunity to change these outcomes. Recent NCI-supported research has demonstrated that there is a long time period—more than 11 years—between the first cancer-related mutation in a pancreatic cell and the development of a mature pancreatic tumor. This means that with the right tools for detection and targeted treatments, pancreatic cancer could be diagnosed while it is surgically curable.

Both NCI's research portfolio and the fiscal year 2011 strategic plan for pancreatic cancer reflect several specific goals, including:

—in-depth gene sequencing of pancreatic tumors to develop tools for detection and treatment;
—identification of genetic factors, environmental exposures, and gene-environment interactions that contribute to the development of this cancer;
—identification and development of biomarkers to allow early detection;
—improvement in our ability to detect tumors when they are much smaller than those currently able to be detected with our imagining capabilities; and
—development of effective targeted therapies.

To accomplish these goals, NCI is supporting a breadth of research across its portfolio that applies to the scientific underpinnings of all of these goals, including in-depth sequencing of pancreatic tumors through The Cancer Genome Atlas. But it is also important to note that advances in oncology that have great benefit for a particular type of cancer do not necessarily flow from research specifically on that cancer type. For example, investment in a rare disease, retinoblastoma, was critical for the discovery of tumor suppressor genes, a class of genes that is altered in essentially every cancer. Similarly, work on an animal model of neuroblastoma led to the discovery of an oncogene, HER2, which is targeted by antibodies now widely used in the treatment of breast cancer. Thus, while it is crucial for the NCI to give full attention to the clinical consequences of every cancer type, we must also be responsive to opportunities and ideas that seem likely to offer the best chances of making discoveries that bring us closer to understanding all cancers, as well as individual cancer types.

QUESTIONS SUBMITTED BY SENATOR BARBARA A. MIKULSKI

CANCER GENOME ATLAS

Question. Dr. Varmus, please provide an update on how The Cancer Genome Atlas (TCGA) is proceeding and how it is contributing to reaching the goal of precision medicine that was described in the 2011 Institute of Medicine report, "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease."

Answer. TCGA, a joint effort of the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), is the largest and most comprehensive analysis of the molecular basis of cancer ever undertaken. Through the application of genome analysis technologies, including large-scale genome sequencing, TCGA is beginning to provide a comprehensive foundation of the abnormalities associated with the tumor types under study, the degree to which tumors within each type are similar and distinct, and the degree of overlap between tumor types. This foundation has the potential of improving our ability to diagnose, treat, and prevent cancer, providing an important element in reaching the goal of precision medicine.

TCGA began as a pilot project in 2006, studying cancers of the lung, brain (glioblastoma) and ovary, and it has been expanded over time to include additional tumor types. Currently in the third year of its post-pilot phase, TCGA has begun the comprehensive analysis of 16 additional cancers including breast, colorectal, kidney, lung, endometrial, and pancreatic cancers, among others. Of these projects, one-quarter are published or in manuscript form; one-quarter are in late-stage analysis; and the remaining one-half are still being collected and studied, with TCGA on track to conclude this phase in 2014. TCGA has also initiated a small project on rare tumors, with plans to complete initial discovery by the end of this year.

TCGA's efforts to advance the understanding of the molecular basis of cancer are already providing the biological insights considered critical by the 2011 report, "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease," to reaching the goal of precision medicine. The report, produced by the National Research Council of the National Academy of Sciences, and sponsored by the National Institutes of Health, identifies a "knowledge network of disease" as necessary to enable a new taxonomy of disease that integrates molecular and clinical data, as well as health outcomes. TCGA's findings, as well as other work supported by the NCI's Center for Cancer Genomics, are poised to contribute directly to this network. The NCI is taking a leadership role in advancing precision medicine in cancer, and in April 2012 hosted a workshop that brought together NCI scientists and colleagues from across the cancer community to consider ways in which NCI can support the acceleration of precision medicine to cancer research and treatment.

ANGIOGENIC LEVELS

Question. Dr. Collins, what work is NIH conducting to help establish baseline angiogenic levels in healthy individuals and those with disease? How will this work impact NIH's ability to measure the effects of diet on blood vessel development?

Answer. NCI funds angiogenesis-related research that includes examination of cancer-related angiogenesis and exploration of therapies targeting this process, as well as research on diet, angiogenesis, and cancer prevention. Research is also underway to investigate the effect of moderate intensity exercise on blood vessels. Angiogenesis, and specifically research measuring the effects of diet on blood vessel development, is an area of research the NCI continues to support. Two examples of ongoing NCI research related to angiogenesis include:

—An examination of the underlying mechanisms for the association between increased physical exercise and decreased risk of several types of cancer and the effects of exercise on angiogenesis-related biomarkers in serum.

—A diagnostic imaging study examining baseline tissue angiogenic markers and the outcomes of chemotherapy delivered directly to liver tumors via a catheter (transarterial chemo embolization therapy).

STRATEGIC SCIENTIFIC PLAN

Question. Dr. Collins, NIH has published a Request for Information seeking comments on the Strategic Scientific Plan for the proposed new Substance Use and Addiction Disorders Institute. Does NIH intend to provide access to these comments to the scientific community and the general public? Will NIH make all of the responses available to the public as they are received?

Answer. The Request for Information seeking input into the Scientific Strategic Plan is open through May 11, 2012. NIH will provide access to all of the responses after the comment period closes. NIH will also provide a summary of the comments after completing an analysis of the responses.

QUESTIONS SUBMITTED BY SENATOR RICHARD C. SHELBY

NATIONAL CHILDREN'S STUDY

Question. Dr. Collins, I am hearing serious concerns from the research community regarding proposed changes to the National Children's Study (NCS). The study was originally designed around a representative door-to-door sampling of the U.S. population and now the sampling strategy has been significantly changed to be based on provider locations instead.

How much input did you receive from the scientific community and in particular the principal investigators participating in the study and your advisory committee, on the changes being made to the sampling strategy?

Answer. The change in the NCS Study design is being considered primarily for scientific reasons but also with awareness of our need to be fiscally responsible. It is based on data generated during the ongoing Vanguard, or pilot phase, of the NCS. The Vanguard data showed that the proposed study design would not enroll sufficient numbers of families within a scientifically acceptable timeframe or within a fiscally sound budget. Pilot testing conducted through the Vanguard sites showed that a study design based primarily on recruiting participants through healthcare providers was most efficient and could offer scientific advantages that would more than offset its scientific compromises. This provider-based approach also has been employed effectively in other large Federal studies. The President's fiscal year 2013 budget request, which shows a reduction of approximately 15 percent, to $165 million annually, for the NCS, appropriately reflects these proposed design changes.

As currently envisioned, the NCS Main Study would use a provider-based participant selection and recruitment strategy that the National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality have both employed effectively in other studies. This approach uses research ready healthcare provider networks as the primary source for recruitment. The NCS would gain additional participants through the award of contracts for supplemental recruitment from secondary sources (such as title V clinics, Indian Health Service clinics, or contract research organizations) to assure inclusion of appropriate population groups, specifically those with health disparities. The use of these two coordinated selection and recruitment strategies would improve the quality of the Main Study and allow analyses not feasible with either approach alone.

If adopted, this revised approach would offer several advantages, including:

—greater recruitment efficiency;

—leveraging access to consenting participants' electronic health records, thus improving the amount and consistency of data collected while lowering costs;
—the potential to leverage the existing infrastructure of networks of healthcare providers, again improving the quality of data and lowering costs; and
—allowing built-in continuity for participants who move but remain within the provider network (many provider networks have statewide or regional coverage) or join another provider network affiliated with the Main Study.

NCS continues to refer to the Institute of Medicine (IOM) report that was written by a panel of experts convened to review the original study design. Many of the changes recommended in the report have already been addressed, including the need for an ongoing Vanguard Study to test the study protocol and scientific methodology. The report also noted that the large number of field contractors was a weakness of the Study design, and the NCS is moving to correct this weakness.

The National Children's Study Advisory Committee meets at least four times a year; the April 24, 2012 meeting was the 32d meeting of the committee. These meetings are open to the public, and a public comment period is provided. Presentations to the Advisory Committee also are posted on the NCS Web site. As they have become available, data from the Vanguard Study have been presented at each of the committee's meetings. The topic of a provider based approach to Study recruitment was discussed twice in the last year with the Advisory Committee, first in April 2011 and then again in July 2011, before being the focus of the entire April 24, 2012 meeting. The NCS Study Director holds weekly national conference calls for Vanguard Study contractors to update them on recent developments and to receive their input. The investigators also provide expertise and comments through a monthly Executive Steering Committee meeting, through 2-day face-to-face meetings every 6 months, through circulation of all study instruments and protocol changes to all investigators for comment, and through a mailbox account dedicated to contractors.

Question. How will the academic community be involved going forward?

Answer. Current NCS Vanguard Study contracts expire over the next 17 months. All Requests for Proposals for both the Vanguard and Main Studies will have full and open competitions. Academic institutions can offer proposals for new Study contracts for primary data collection, and have other options as well, including partnering with a primary data collector, conducting ancillary studies using NCS infrastructure, or doing their own research analyses using NCS data as they become available.

In addition, the NCS holds workshops and conferences several times a year and holds open Advisory Committee meetings on a quarterly basis to which the academic community is welcome. NCS also meets with professional societies and other organizations on an ongoing basis and NCS personnel plan and attend academic meetings throughout the year.

Question. In 2010, the committee was informed by NIH that the approximate cost of the entire NCS program would double—from $3.1 to $6 billion. Now, you are cutting the request by 15 percent. The budget justification provides no details on how you arrived at the request amount for fiscal year 2013. Can you lay out, specifically, how the $165 million request was reached?

Answer. NCS is able to reduce overhead costs through greater operational efficiencies and redistribution of tasks and responsibilities. Examples include the use of nonproprietary software to eliminate license fees and proprietary support; use of a federated model for human subject protection to reduce redundancy and speed approvals through elimination of duplicate administrative resources; use of the NCS program office as a coordinating center to develop study instruments and protocol documents, to perform data analysis, and to manage field operations and general consolidation of overlapping field operations.

With the reduction in overhead, we anticipate that for fiscal year 2013 we need about $35 million for support services and about $130 million for ongoing Vanguard operations and Main Study initiation.

Question. Why are there no longer any study hypotheses which address the congressional concerns for the NCS put forth in the Children's Health Act of 2000?

Answer. As directed by the Children's Health Act of 2000, the NCS is a longitudinal birth cohort study with the overall goal of examining the role that environmental influences (including physical, chemical, biological, and psychosocial) have on children's health and development. Hypotheses about what factors affect children's health and development will inform the questions asked and the data collected for the Study, but the NCS will not be hypothesis-driven. Children's environments are likely to change substantially over the next two decades, and our goal is to create the richest possible data, biospecimen, and environmental specimen resource to answer important questions about health and development as they arise.

Question. It is my understanding that the new proposal will move the sampling scope from a door-to-door model to a health maintenance organization-based model. By design, this would exclude involvement of the uninsured and likely the involvement of rural and minority populations. These populations are a critical component to achieving scientifically valid findings. How will you address this issue?

Answer. As currently envisioned, the NCS Main Study would use a provider-based participant selection and recruitment strategy that the NIH and the Agency for Healthcare Research and Quality (AHRQ) have both employed effectively in other studies. This approach uses research ready healthcare provider networks as the primary source for recruitment. The NCS would gain additional participants through the award of contracts for supplemental recruitment from secondary sources (such as title V clinics, Indian Health Service clinics, or contract research organizations) to assure inclusion of appropriate population groups, specifically those with health disparities. The use of these two coordinated selection and recruitment strategies would improve the quality of the Main Study and allow analyses not feasible with either approach alone.

Question. The Vanguard Centers have created nearly a decade's worth of research infrastructure including costly "build outs" of field office space composed of laboratories for processing biological and environmental specimens, and call centers. These facilities were built to detailed specifications provided by the NCS program office. Other NCS research infrastructure include the hiring, certifying and training of staff, development of a Federated Institutional Review Board, and establishment of a Federal Information Security Management Act compliant environment. In addition, the Vanguard Centers have spent years developing cooperative agreements and memoranda of understanding with countless delivery hospitals to ensure that NCS participant biological and medical data can be obtained at the time of birth. Given the newly proposed design of the NCS, it appears as though this infrastructure could go to waste without utilizing the resources of the existing Vanguard Centers. What assurances can you provide that these Vanguard Centers will be eligible to compete for continued participation in the NCS and be afforded a reasonable, full, and fair opportunity to do so?

Answer. The Vanguard Study will continue to pilot study methods in its current 40 locations, several years in advance of the Main Study, following the children already recruited by the Vanguard Study until they turn 21. In this follow-up phase, it will use a smaller number of contractors than in its earlier recruitment phase, thus following recommendations in the IOM report from 2008 and realizing cost savings, while improving scientific quality by achieving greater consistency in data and specimen collection among study sites.

Current NCS Vanguard Study contracts expire over the next 17 months; new contracts will be awarded following full and open competitions. The NCS is working with current contractors to ensure the orderly transition of data collection services and of relationships with participants, communities, and other local institutions. As is usual with longitudinal studies that extend across many years, individual contractors may continue to change during the course of the study, and it is important for the NCS to have procedures in place to ensure smooth transitions that may occur in the future.

All Requests for Proposals for both the Vanguard and Main Studies will have full and open competitions. Academic institutions can offer proposals for new Study contracts for primary data collection, and have other options as well, including partnering with a primary data collector, conducting ancillary studies using NCS infrastructure, or doing their own research analyses using NCS data as they become available. Finally, contractors that complied with NCS specifications for field operations will have established a platform that is flexible and adaptable to multiple uses, so they can leverage that investment for additional projects.

DRUG RESCUE AND REPURPOSING

Question. Dr. Collins, at the NIH hearing last year, we discussed drug rescue and repurposing—that is, leveraging existing compounds to develop new, novel treatments for patients. In January, NIH released a concept for a program called the Drug Rescue Program to fund research to identify new therapeutic uses of proprietary investigational drugs and biologics. I am pleased to see NIH moving forward on this issue since it is an ideal opportunity for academia to team with industry to bring treatments to patients faster. However, repurposing compounds brings up a number of challenges, including concerns regarding intellectual property rights and liability. In particular, will pharmaceutical companies be interested in repurposing drugs they currently make money on if a new patient population could open them up to new lawsuits? How will you address these concerns?

Answer. In early May, National Center for Advancing Translational Sciences (NCATS) expects to establish a pilot collaborative drug rescue program, Discovering New Therapeutic Uses for Existing Molecules, to match researchers with a selection of industry-developed molecular compounds in an attempt to identify a therapeutic use. These compounds are currently not approved for any use and are not being pursued by the pharmaceutical company. The program will incorporate innovative template agreements designed to streamline the legal and administrative process for participation by multiple organizations. These templates will reduce time, cost, and effort, as well as enable greater participation than traditional partnerships. The templates also provide a roadmap for handling intellectual property used in or developed through the program. Participating industry partners will retain the ownership of their compounds, while academic research partners will own any intellectual property they discover through the research project with the right to publish the results of their work.

This pilot program will focus on drug rescuing only. It does not include drug repurposing, which is an attempt to find a new use for a drug that is already approved for another therapeutic use. NCATS is considering how best to structure initiatives which enable drug repurposing, with the understanding that repurposed drugs would undergo the same Federal Drug Administration (FDA) requirements and clinical development investments as newly developed compounds and will need to meet FDA patient safety and efficacy requirements.

HEALTH ECONOMICS

Question. Dr. Collins, the President's budget requests $13 million from the Common Fund for health economics research. Diverting biomedical research funds to pay for health economics research is not only a significant departure from traditional NIH research funding but also duplicative of AHRQ health economics research and the Center for Disease Control and Prevention research on the economics of prevention. For example, one of the programs four major initiatives in the budget request is for a program entitled: "The Science of Structure, Organization, and Practice Design in the Efficient Delivery of Healthcare." This initiative appears directly duplicative of AHRQ's existing program, the Patient-Centered Health Research/Effective Health Care, that seeks to conduct research around the same areas on healthcare delivery and efficiency. Since AHRQ's mission seems more appropriately suited toward researching the economics and efficiency of healthcare delivery, why should we be taking money away from valuable investments in biomedical research, when much of this work appears to be in progress within other Health and Human Services Operating Divisions?

Answer. We are working with AHRQ and other agencies to collaborate on this critical issue to ensure that NIH research does not conflict with their efforts and missions. NIH's mission is "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability." We initiated this Common Fund program in Health Economics as a way to measure the success of the translation of the benefits of our research into enhanced health of the U.S. population.

Much of the NIH research enterprise generates optimism that a new era of personalized medicine (meaning both prevention and treatment) will lead to improved outcomes while keeping cost growth under control. For this promise to be realized, we will need to understand the reasons organizations and individuals adopt new approaches.

QUESTIONS SUBMITTED BY SENATOR LAMAR ALEXANDER

CLINICAL AND TRANSLATIONAL SCIENCE AWARDS

Question. The largest single Federal grant at Vanderbilt University is a clinical and translational science award (CTSA) for approximately $50 million. Vanderbilt is also the national coordinating center for all of the CTSA's. How do you see the interactions between the CTSAs and the rest of the National Center for Advancing Translational Science (NCATS) developing, and what is being done to support a high level of interaction?

Because of the shortage of products in the drug pipeline, do you see NCATS as more focused on drug development, or will the CTSAs also continue to be able to build on the programs of training, career development for young investigators, research informatics, community engagement, and clinical research infrastructure? All of these are still important for biomedical research.

Answer. With the creation of NCATS on December 23, 2011, the administration of the CTSA program moved into a new home. Within NCATS, the program will continue to support the highest quality translational research. Now as part of a new division, the Division of Clinical Innovation (DCI), the CTSA program is benefiting from adjacency to the new Division of Preclinical Innovation (DPI). DPI includes programs that focus on re-engineering the early phases of translation (including assay development, high-throughput screening, lead optimization, and predictive toxicology) as well as the Therapeutics for Rare and Neglected Diseases program. A fully integrated program will be put in place so that the DPI and the DCI are truly a single effort guided by a shared mission.

One of the great successes of the CTSA program has been its development of training programs for clinical researchers and allied professionals in the many aspects of translational science. As the CTSA program incorporates the mission of NCATS, this emphasis on training will be sustained and expanded to build in specific areas of need, such as informatics and pharmacology. We anticipate that the CTSAs will have an important role in facilitating first-in-human trials for new therapies, promoting innovation in research methods, and re-engineering the processes for clinical research. We expect that they will continue to provide a home for community outreach and education at institutions across the country. The CTSA program will continue to support the entire spectrum of translational research, evolving to meet the most pressing scientific needs and opportunities. NCATS is not a drug development center; its broader mission is to enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of diseases and conditions.

PERSONALIZED MEDICINE

Question. The physicians and researchers at Vanderbilt are investing a great deal in the science of personalized medicine. Can you tell us what the term "personalized medicine" means to you, and what role you see for National Institutes of Health (NIH)?

Answer. Personalized medicine, or more precisely "genomic medicine," is the medical application of genomics for the purposes of disease prevention, diagnosis, and treatment. It is sometimes referred to as "precision medicine" or "individualized medicine." Through genomic medicine, we will anticipate and often pre-empt the onset of disease, diagnose disease more quickly and accurately, and tailor the choice of medications according to an individual's genomic information.

This vision for improved healthcare tools and options was a key driving force behind the Human Genome Project (HGP; http://www.genome.gov/10001772)—a major international project led by the NIH. Scientists recognized that, in order to realize genomic medicine, we would first need much more detailed knowledge of the human genome. Through the HGP, scientists were able to determine the full molecular sequence of the human genome and its genes.

NIH, led by the National Human Genome Research Institute (NHGRI), is now building on the success of the HGP. In 2011, NHGRI published a new strategic vision describing the research path necessary for genomic medicine to become reality (http://www.genome.gov/sp2011/). The plan emphasizes that a deeper understanding of the basic biology of the genome, such as identifying all its functional elements and how genomes vary from person to person is needed. It also highlights the need to investigate how genome variation influences health and disease and the work to be accomplished to explore the clinical applications of genomics. NIH is now leading this research through cutting-edge programs and research initiatives.

For instance, NHGRI and the National Cancer Institute collaboratively lead "The Cancer Genome Atlas" to better understand the molecular basis of cancer. NHGRI also is funding research to detect the genetic underpinnings of thousands of rare diseases for which there is no known cause, as well as undertaking a major project to investigate the genetic causes of Alzheimer's disease. While it will be many years before genomics is fully incorporated into patient care, NHGRI-funded researchers are investigating the clinical use of genomics in patients at risk for many diseases, including those with mysterious conditions that have long eluded diagnosis. Institutes and Centers (ICs) across NIH are conducting genomic research to elucidate the genomic causes of disease and how the genome influences the effectiveness of treatment.

Though sometimes envisioned as a phenomenon of the future, genomic medicine is already having an impact on how patients are treated. This is especially true in the field of pharmacogenomics, where drug selection and administration increasingly is assisted by prior genetic testing. The Food and Drug Administration now lists approximately 100 approved drugs with pharmacogenomic information on their

labels. These include abacavir, now the standard of care for HIV-infected patients, as well as drugs for the treatment of cancers, clopidogrel for treating cardiovascular disease, and warfarin for preventing blood clotting.

Genomics is also being used to help patients who do not respond to conventional treatment. An example of this was described by NIH Director Francis Collins, M.D., Ph.D. during his testimony before the subcommittee during the NIH hearing on March 28. Dr Collins told the story of twins Alexis and Noah Beery, who suffered from a rare and devastating movement disorder called dystonia. The causative mutation was identified through sequencing of their genomes, after which their treatment was changed and their health improved remarkably.

Genomics promises to advance healthcare over the next several decades. NIH will continue to lead the way toward genomic medicine through funding and conducting the pioneering science that will be necessary to realize the full potential of genomic medicine.

DIABETES

Question. Diabetes continues to be a costly and growing epidemic for Tennessee and the United States. Dr. Collins and Dr. Rodgers, can you tell us how NIH, and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in particular, are addressing this epidemic?

Answer. NIH and NIDDK are working to develop and test prevention and treatment strategies for type 1 and type 2 diabetes through a robust research program that supports basic, clinical, and translational research, as well as research training. Future research will be guided by a strategic plan for diabetes research that was recently released by the NIDDK (http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/DiabetesPlan/PlanPosting.htm). Landmark clinical research supported by the NIH has included the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study, which established the value of tight blood glucose control in reducing complications in type 1 and type 2 diabetes respectively; and the Diabetes Prevention Program, which proved that type 2 diabetes can be prevented or delayed through delivery of an intensive lifestyle intervention, or, to a lesser degree, with the generic drug metformin. Knowledge from NIH diabetes research is communicated to patients, health professionals, and the public through the National Diabetes Information Clearinghouse and the National Diabetes Education Program.

In 2011, NIDDK completed the first major trial of type 2 diabetes management in children and adolescents, a newly emerging problem, and demonstrated that intensive glucose control in people with type 1 diabetes can reduce rates of chronic kidney disease and end-stage renal disease by 50 percent 22 years later. NIDDK supported planning grants for a comparative effectiveness clinical trial testing different medications, in combination with metformin, for type 2 diabetes treatment, and for a clinical trial testing vitamin D in prevention of type 2 diabetes based on a promising pilot study. Other clinical trials include Action for Health in Diabetes (Look AHEAD), to determine the value of a lifestyle intervention for improving diabetes outcomes, and investigation of bariatric surgery as treatment for diabetes, complemented by studies in animal models.

New initiatives are fostering research toward preserving function of insulin-producing beta cells early in the course of type 2 diabetes, and a new consortium was launched to study approaches to prevent gestational diabetes. The Beta Cell Biology Consortium identified a potential new strategy to induce beta cell regeneration to replace lost beta cells and reverse aging-associated decline in beta cell growth. NIDDK is also working to understand and ameliorate disparities in diabetes with research to identify gene regions conferring type 2 diabetes risk in multiple ethnic groups, translational research to bring scientific discoveries to all who can benefit, and a clinical trial of type 2 diabetes management including minority youth and adolescents.

MINORITY HEALTH AND HEALTH DISPARITIES

Question. Dr. Collins, the healthcare reform law clarified the role of the National Institute on Minority Health and Health Disparities (NIMDH) at NIH as it pertains to coordinating health disparities research. How are you and the IC Directors going to work together to make the newly elevated NIMHD the coordinating body at NIH on health disparities?

Answer. The law clearly identifies the NIMHD as the coordinating body for minority health and health disparities at NIH. The NIH Institutes and Centers will continue to administer their programs on minority health and health disparities and work with the NIMHD as required in its coordinating role.

Question. Where does the NIH stand in terms of funding that is allotted to minority health and health disparities? In the last strategic plan, there was $2.5 billion being spent on minority health and health disparities at various ICs. What is that amount now, and how are you going to work with the new health reform law so that the NIMHD is the coordinating entity at NIH for these issues?

Answer. The overall NIH fiscal year 2011 funding for health disparities was $2.7 billion. NIMHD recently hired a Deputy Director for strategic scientific planning and program coordination, who will lead the NIMHD coordination of minority health and health disparities working with the Institutes and Centers.

Question. Considering last year's NIH study, which showed possible bias against African Americans with the awarding of NIH R01 grants, will you work with Meharry Medical College and the Association of Minority Health Professions Schools to ensure their annual health profession pipeline symposium, exposing hundreds of students to the health professions, receives adequate funding?

Answer. A working group of the National Advisory Council (ACD) has been working on this vexing problem and is scheduled to report its recommendations at the June 14 meeting of ACD. The president of Meharry Medical College, Dr. Wayne Riley, is a member of this working group. As part of this deliberative process, outreach efforts have included many of the institutions represented by the Association of Minority Health Professions Schools (AMHPS). Meharry Medical College and the AMHPS have successfully competed in the past for NIH funding to support the annual health professions symposium, and are encouraged to continue applying for NIH funding. Several of the NIH Institutes and Centers have contributed funds to support the symposium.

Question. The NIH has issued two strategic plans and budgets to reduce and eliminate health disparities since the Congress enacted the legislation requiring it. What is the status of the next strategic plan?

Answer. The NIH Health Disparities Strategic Plan and Budget fiscal year 2009–2013 has been approved and is available on the NIMHD Web site at http://www.nimhd.nih.gov/about__ncmhd/index2.asp.

Question. Can you provide detailed funding information for minority health and health disparities activities at the NIH broken out programmatically by Institute and Center?

Answer. The NIH Health Disparities Strategic Plan and Budget fiscal year 2009–2013 provides information on programs/activities by Institutes and Centers with associated budgets for each goal by IC and is available on the NIMHD Web site at http://www.nimhd.nih.gov/about__ncmhd/index2.asp.

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

INTERSECTION OF NATIONAL CANCER INSTITUTE AND NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCE

Question. We have heard Dr. Collins and others discuss the value to National Institutes of Health (NIH) of the newly created National Center for Advancing Translational Science, or (NCATS). NCATS is being positioned to become a resource that will support the translational research work across all of NIH's Institutes and Centers.

Could you clarify how the National Cancer Institute (NCI) will work with NCATS to optimize the investments that will be made in NCATS and the knowledge that will be developed in this new center?

Answer. Translational research supported by NCI transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality—it is a critical piece of the NCI's research portfolio and encompasses numerous programs and funding mechanisms.

For example, researchers working in NCI's Specialized Programs of Research Excellence (SPOREs) and investigator initiated Program Project (P01) grants at NCI-supported research institutions across the country, conduct promising translational research. The NCI Drug Discovery and Development Program, run through the Frederick National Laboratory for Cancer Research, has successfully guided drug candidates through the final steps of development to first-in-human studies. The Cancer Genome Atlas (TCGA) and Therapeutically Applicable Research to Generate Effective Treatment (TARGET) programs are generating data on the genomic foundations of cancer, and the Cancer Target Discovery and Development (CTDD) Network is accelerating the transition of molecular data from initiatives like TARGET and TCGA to new treatments through gene validation studies as well as high-throughput screening of small molecules.

NCATS will complement these efforts, particularly by providing resources and infrastructure to assist the basic research community in moving their discoveries to the next phase. NCATS will work to improve the methodology of translational research, and will also collaborate with and utilize NCI programs in the process. There will be points where NCI and NCATS intersect to share knowledge and technology. For example, Clinical and Translational Science Awards (CTSA) are an initiative funded principally by NCATS. Most academic institutions that have an NCI-designated Cancer Center also have a CTSA and many collaborative projects have emerged from these synergies.

VALUE OF CANCER CENTERS

Question. I have had the opportunity to visit a cancer center in my home State—The University of Kansas Cancer Center. I have seen basic research at work in impressive labs. In particular, at the University of Kansas (KU) I have seen how this research is being translated into the development of early phase drugs—in one case through a ground-breaking collaboration between the University of Kansas Cancer Center, NIH, and the Leukemia Lymphoma Society. I believe that collaborations such as this that bring public and private resources and expertise together are important if we are to maximize the return on the investments of our Federal dollars. And last but definitely not least, I have seen patients coming to KU with the ability to participate in clinical trials, with the hope and real potential that the delivery of cutting-edge research into their care may change the course of their disease for the better.

What are the programs at NCI that make this cycle of innovation and translation possible?

Specifically, do you see a specific role for the Cancer Centers program in making sure that this cycle of translation of basic research findings into clinic application continues to take place?

Answer. NCI engages in multiple collaborations along the research continuum, including funding a variety of innovative biotechnology companies via its Small Business Innovation Research program.

The NCI's 66 Designated Cancer Centers, which are distributed in all regions of the United States, play a crucial role in the Nation's cancer research effort and are the primary source of new discoveries about cancer prevention, diagnosis, and treatment. The Cancer Centers deliver state-of-the-art care to patients and their families, inform healthcare professionals and the general public, and often work through partnerships with other healthcare organizations to reach underserved populations. Clinical application—providing prevention, diagnosis, and therapies for patients—is the ultimate goal for all cancer research, and NCI-designated Cancer Centers have a proud history of leadership in clinical trials, many of which have led to changes in the standard of care for cancer patients. Along with the many other NCI-funded research and academic institutions, and NCI's intramural program, they are a major source of new discoveries into cancer's causes, prevention, diagnosis, and treatment.

The NCI-Designated Cancer Centers are required to facilitate the rapid transfer of clinical observations to laboratory experiments, and promising lab-based discoveries to innovative applications in the prevention, detection, diagnosis, treatment, and survivorship of cancer. The Cancer Centers are required to work together and with the NCI to facilitate the translation of fundamental discoveries into tangible patient benefit. For example, researchers at the University of California San Francisco Cancer Center have shown that a molecular test measuring the activity of 14 genes in cancerous lung tissue can improve the accuracy of prognosis and guide treatment options for patients with the most common form of lung cancer. Other recent developments include identification of the first major genetic mutation associated with inherited prostate cancer by researchers from the Johns Hopkins Cancer Center, with implications for the development of genetic tests to identify the mutation and screening practices for men with a family history of prostate cancer. And at the Koch Institute for Integrative Cancer Research at MIT, cancer researchers and engineers are working together to develop more effective drug delivery systems such as nanoparticle "smart bombs" that deliver high concentrations of drugs directly to the cancer cells, a technology currently being studied in a phase I clinical trial.

UPDATE ON NATIONAL CANCER INSTITUTE INITIATIVES

Question. When I read stories about the development of cutting-edge treatments, particularly those that use the body's own immune system to fight cancer and other diseases, I know that we are doing something right to save lives and lower

healthcare costs. Can you explain some of the most promising cancer research opportunities and discoveries that the NCI is currently pursuing?

Answer. NCI supports a diverse research portfolio aimed at increasing our understanding of the genomic foundations of cancer, improving screening technologies, advancing effective treatments including immunotherapies, and developing new approaches for overcoming drug resistance.

Genomic Foundations of Cancer.—Using genomics to match drugs to the patients most likely to benefit from them, and conversely sparing patients courses of treatment from which they will not benefit, promises to be among the new modalities for successfully managing cancer. Understanding the genomic underpinnings of cancer allows for the development of molecularly targeted agents that may be effective against several cancer types, and can often be used in combination with other therapies. NCI's Center for Cancer Genomics, with a mission of developing and applying genome science to better treat cancer patients, coordinates this research area across the NCI.

Screening Technologies.—Tools that can accurately detect and diagnose tumors have potential to markedly improve outcomes for cancer patients since these tools often detect cancer early, before it has spread throughout the body and when treatment is more likely to be curative. Last year, NCI released results from the National Lung Screening Trial indicating that screening with low-dose-computed tomography results in 20 percent fewer lung-cancer deaths among current and former heavy smokers compared with screening with chest xray. This development marks the first time that a screening test has been found to reduce mortality from lung cancer, the most common cause of cancer deaths in the United States and the world. Other initiatives and projects, including a large portfolio of grants, are pursuing biomarkers and imaging techniques with potential to aid in early detection and diagnosis of several types of cancers.

Immunotherapies.—The pace of research advances to stimulate the body's immune system to fight cancer has quickened in recent years, with clinical trials of different therapies showing positive results for several different cancer types. In 2010, data from a large clinical trial established a monoclonal antibody called ipilimumab as the first immunotherapeutic agent to show an increase in survival for patients with advanced melanoma. The drug stimulates the immune system to attack melanoma cells by binding to and inhibiting a molecule called CTLA–4 that is found on the surface of immune cells.

In March 2011, the Food and Drug Administration (FDA) approved the antibody (marketed as Yervoy) to treat late-stage melanoma. NCI-supported research has validated CTLA–4 as a target and has paved the way for studies of the drug for prostate, lung, and renal cancers. Other potentially promising immunotherapy approaches include "adoptive cell transfer," in which T-cells are taken from a patient's tumor, stimulated and reproduced, then put back into the body; and the targeting of "tumor initiating cells" (thought to be the chief cause of cancer recurrences) as well as normal cells that cooperate with cancer cells to help them survive and spread.

Drug Resistance.—One of the most disappointing features of the development of new targeted therapeutics is how routinely drug resistance emerges and the disease begins to progress. Resistance to treatment with anticancer drugs results from a number of factors—every cancer expresses a different array of drug-resistance genes, and various mechanisms have evolved as protection from toxic agents. As therapy has become more effective, acquired resistance has become common. NCI is aggressively pursuing research to gain an understanding of the mechanisms that lead to drug resistance and is looking for agents that overcome these mechanisms. NCI is supporting studies of combination therapies for patients whose disease has become resistant to therapy, as well as exploring alternative approaches through the Provocative Questions Initiative to determine if controlling rather than killing cancer cells can avoid the development of drug resistance.

Question. Also, since NIH's work has been managed over the past few years with flat and decreased funding when you account for inflation, what innovative strategies have you found, or do you plan, that will allow NIH to continue making research progress in this challenging budgetary environment?

Answer. NCI is employing a number of innovative strategies to ensure efficient stewardship of the Nation's investment in cancer research, particularly in the face of stagnant budgets. As mentioned at the recent subcommittee hearing, the Provocative Questions (PQ) project is one creative approach that contributes to this goal. The project is assembling a list of important but nonobvious questions that will stimulate the NCI's research communities to use laboratory, clinical, and population

sciences in especially effective and imaginative ways. While this initiative does not replace the NCI's longtime and essential emphasis on funding investigator-initiated research, it represents a useful new approach to making the greatest impact with our research dollars. Reductions in funding tend to prompt all parts of the research community to become more conservative, often converging on similar subjects, narrowing research portfolios. By pooling the imaginations of the research community to address understudied areas, an initiative such as PQ provides a venue for innovative approaches even in times of fiscal constraint.

Another area where NCI is making strategic changes is its Clinical Trials Cooperative Groups program. Clinical trials are a critical step in moving potential therapies into clinical practice, and the Cooperative Groups are an essential part of this process. The groups are now being reorganized, consolidating nine adult groups into four, with the Children's Oncology Group remaining a separate group. The consolidation is an effort to streamline the development and execution of trials, while continuing to select and prioritize trials through stringent peer review, and to fund the most promising and innovative studies. This process will reduce redundancy and improve the effectiveness and efficiency of trials; and will also result in simplified and better harmonized operations centers, data management centers, and tumor banks. The streamlined framework will also foster a more collaborative approach to selecting the most important trials to perform.

NCI is also changing the way it conducts early phase clinical research. Over the last several years, NCI has developed the ability to do "proof of mechanism" studies, which allow the research community to understand early on whether a drug hits its target. This work defines patient populations that are most likely to benefit from targeted therapies as early in the process as possible. Continued progress in this area will lead to clinical research models that are not only more efficient, but more effective in identifying the appropriate treatment approach for specific patient populations. These are just a few examples that demonstrate NCI's strategic approaches to continue to make progress in a challenging budgetary environment.

Question. The Cancer Genome Atlas (TCGA) is one of NIH's most prominent examples of research growing out of the HGP and is the basis for much of the work taking place today that explores the genomic foundations of cancer. Researchers are working to increase our understanding of the genetic basis of various forms of cancer and how to best capitalize on these genomic breakthroughs. Can you provide an update on how TCGA is proceeding and how this project is contributing to advancements in precision medicine?

Answer. TCGA, a joint effort of the NCI and the National Human Genome Research Institute (NHGRI), is the largest and most comprehensive analysis of the molecular basis of cancer ever undertaken. Through the application of genome analysis technologies, including large-scale genome sequencing, TCGA is beginning to provide a comprehensive foundation of the abnormalities associated with the tumor types under study, the degree to which tumors within each type are similar and distinct, and the degree of overlap between tumor types. This foundation has the potential of improving our ability to diagnose, treat, and prevent cancer, providing an important element in reaching the goal of precision medicine.

TCGA began as a pilot project in 2006, studying cancers of the lung, brain (glioblastoma) and ovary, and it has been expanded over time to include additional tumor types. Currently in the third year of its post pilot phase, TCGA has begun the comprehensive analysis of 16 additional cancers including breast, colorectal, kidney, lung, endometrial and pancreatic cancers, among others. Of these projects, one quarter are published or in manuscript form; one quarter are in late-stage analysis; and the remaining one-half are still being collected and studied, with TCGA on track to conclude this phase in 2014. TCGA has also initiated a small project on rare tumors, with plans to complete initial discovery by the end of this year.

TCGA's efforts to advance the understanding of the molecular basis of cancer are already providing biological insights considered critical to reaching the goal of precision medicine. The work supported by NCI's Center for Cancer Genomics, including not only TCGA but also CTDD and Therapeutically Applicable Research to Generate Effective Treatments (TARGET), will contribute to the advancement of precision medicine.

Question. Last year, the Journal of Oncology published an article entitled "Tumor Angiogenesis as a Target for Dietary Cancer Prevention" examining the suppression of tumor growth by controlling blood vessel growth through diet. I understand that promoting healthy blood vessel growth may have applications in not only fighting cancer but also Alzheimer's disease, arthritis, and cardiovascular disease. I also understand that evaluating baseline angiogeneic levels in healthy individuals and those with disease are critical to measuring the effects of diet on blood vessel development. What work is NIH conducting to help establish baseline angiogenic levels?

Answer. NCI funds angiogenesis-related research that includes examination of cancer-related angiogenesis and exploration of therapies targeting this process, as well as research on diet, angiogenesis, and cancer prevention. Research is also underway to investigate the effect of moderate intensity exercise on blood vessels. Angiogenesis, and specifically research measuring the effects of diet on blood vessel development, is an area of research the NCI continues to support. NCI's Division of Cancer Prevention is considering hosting a workshop to bring together experts in angiogenesis and nutrition to explore current science regarding angiogenesis modification, diet, and cancer. Two examples of ongoing NCI research related to angiogenesis include:

—an examination of the underlying mechanisms for the association between increased physical exercise and decreased risk of several types of cancer and the effects of exercise on angiogenesis-related biomarkers in serum; and

—a diagnostic imaging study examining baseline tissue angiogenic markers and the outcomes of chemotherapy delivered directly to liver tumors via a catheter (transarterial chemo embolization therapy).

SUBCOMMITTEE RECESS

Senator HARKIN. Thank you all very much.

[Whereupon, at 11:54 a.m., Wednesday, March 28, the subcommittee was recessed, to reconvene subject to the call of the Chair.]