DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2014

WEDNESDAY, MAY 15, 2013

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

The subcommittee met at 2:30 p.m., in room SD–138, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.

Present: Senators Harkin, Mikulski, Moran, Cochran, Shelby, and Boozman.

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

GARY H. GIBBONS, M.D., DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

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

STORY C. LANDIS, Ph.D., DIRECTOR, NATIONAL INSTITUTE FOR NEUROLOGICAL DISORDERS AND STROKE

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

OPENING STATEMENT OF SENATOR TOM HARKIN

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

Today, we are privileged to have with us, again, as my longtime compatriot Arlen Specter used to say, "The crown jewel of the Federal Government." That is our National Institutes of Health (NIH) here today for our budget hearing.

So, Dr. Collins, we welcome you back to the subcommittee, and also, in alphabetical order, Dr. Tony Fauci, Director of the National Institute of Allergy and Infectious Diseases; Dr. Gary Gibbons, Director of the National Heart, Lung, and Blood Institute; Dr. Richard Hodes, Director of the National Institute on Aging; Dr. Story Landis, Director of the National Institute for Neurological Dis-

orders and Stroke; Dr. Harold Varmus, Director of the National Cancer Institute.

This is a perilous moment for NIH and, indeed, for the future of biomedical research in this country. Since fiscal year 2003, the end of the 5-year doubling effort, NIH funding has dropped in real terms by 22 percent. In other words, the purchasing power of NIH's appropriations has fallen by more than one-fifth over the past decade.

This year, fiscal year 2013, NIH funding will drop in actual dollars by $1.7 billion below last year's level, almost entirely because of sequestration.

As a result, NIH will award 700 fewer new research project grants this year than it did last. That means 700 fewer opportunities to investigate and possibly find the cures for cancer and Alzheimer's and diabetes and any number of diseases.

Perhaps even more alarming, a researcher's chance of getting a grant approved by NIH will drop to just 16 percent. That is the lowest success rate in the history of NIH.

That comes at the time when the potential for scientific breakthroughs has perhaps never been better. At the National Cancer Institute, the success rate will be just 12 percent. At other institutes, below 10 percent. That's abysmal.

When you have less than a 1-in-10 chance of getting a grant, that's when our best and brightest young minds start asking, "What's the point? Maybe I need to find a different career."

It's no wonder that some are saying our Nation's status as the undisputed world leader in biomedical research is under threat.

The President's budget request offers a welcome response to this disturbing decline. His budget calls for $31.1 billion for NIH in fiscal year 2014, which would not only reverse all of the cuts that are occurring this year but result in an increase over the fiscal year 2012 level. Included in that increase is $40 million to the new Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which I'm sure we'll hear more about.

And I read your testimony last night, you mention that, both Dr. Collins and, I'm sure, Dr. Landis.

So I want to do everything I can to help boost NIH's budget this year. I suspect that many Senators on the other side of the aisle also agree with this. NIH enjoys more bipartisan support than perhaps any other Agency in the entire Labor-HHS appropriations bill.

But here's a problem. At the same time some of my colleagues are requesting a strong commitment to NIH funding, they also want sequestration to continue in fiscal year 2014. Some even want deeper cuts to nondefense discretionary spending next year to pay for some more increases in defense spending.

There simply is no way to square these two priorities. I can promise you, if sequestration stays in effect next year, there's no chance that we will get close to the President's request for NIH, let alone back to the fiscal year 2012 level. It just won't happen.

We are not going to savage other functions in education, health, labor, Centers for Disease Control and Prevention, and others, which are already at minimal levels. I will not get engaged in pitting NIH against other worthwhile endeavors in this appropriations bill.

This is just one of the many reasons why we need to replace sequestration with a mix of targeted, responsible spending cuts, not just blind cuts to everything, and, yes, increased revenue.

This sort of balanced approach is the only way NIH will have the resources it needs to realize the enormous scientific opportunities that we'll hear about shortly from our witnesses.

First, I'll yield to Senator Moran for his opening statement.

STATEMENT OF SENATOR JERRY MORAN

Senator MORAN. Mr. Chairman, thank you very much, and let me thank you and your staff for the continual effort for us to work together to find a path forward on a Labor-H bill. I very much appreciate the attitude and approach that our staffs, and you and I, are taking.

And I appreciate Dr. Collins and the other center directors being here today. This is a highlight, I think, for our subcommittee as we hear of some of the most recent and exciting developments as we face the challenges that disease provides.

Science and research are the foundation of innovation, growth in our economy, and the solution to a myriad of issues that confront the health and well-being of our Nation. NIH funding biomedical research is the catalyst behind many of the advances that are now helping Americans live longer and healthier lives.

Because of the Federal investment in biomedical research, U.S. cancer rates are now falling 1 percent each year, with each 1-percent decline saving our Nation about $500 billion.

The U.S. death rate from heart disease and stroke have declined more than 60 percent in the last half century. And between 1997 and 2006, the death rate among adults with diabetes declined 23 percent.

However, health advances aside, and they are paramount, the reduction of healthcare costs in the future may be one of the most significant contributions to society that medical research provides.

As baby boomers age, the cost of healthcare will continue to increase. For example, a study led by the economists at the RAND Corporation stated that the cost of dementia care is projected to double over the next 30 years, surpassing healthcare expenses for both heart disease and cancer. Without a way to prevent or cure or effectively treat dementia, it will be difficult, if not impossible, to rein in costs.

But science has confronted similar health challenges in the past and has prevailed. In the mid-20th century, economists predicted polio would cost taxpayers $100 billion a year to treat patients in iron lung hotels. In the face of this challenge, medical research produced a solution to this devastating disease, and polio is now on the verge of being eradicated worldwide.

In the next few years, we confront difficult spending choices. And I believe we must prioritize our Federal commitment to NIH. It is crucial that our next generation of biomedical researchers, the ones who will develop better and more cost-effective healthcare, remain in the scientific research field.

Without adequate and sustained Federal support for medical research, trainees will be driven from medical fields, or into the arms of our global competitors.

Last year, China's Government pledged to increase basic research investment by 26 percent and will contribute more than $300 billion to biotechnology over the next 5 years.

PREPARED STATEMENT

In the last 5 years, China's percentage of science and engineering degrees earned by university students was more than double those earned here in the United States. Without continued investment in NIH, we jeopardize our current scientific progress, risk losing a generation of scientists, and stunt our Nation's global competitiveness.

This is not a time to waver on America's commitment to NIH and to the health of all Americans.

Mr. Chairman, thank you, and I look forward to working with you on these priorities.

[The statement follows:]

PREPARED STATEMENT OF SENATOR JERRY MORAN

Thank you, Mr. Chairman. I appreciate Dr. Collins and the other Center Directors being here today to discuss funding for the National Institutes of Health (NIH).

Science and research are the foundation of innovation, growth in our economy, and the solution to the myriad of issues that confront the health and well-being of our Nation. NIH-funded biomedical research is the catalyst behind many of the advances that are now helping Americans live longer and healthier lives. Because of the Federal investment in biomedical research, U.S. cancer death rates are now falling 1 percent each year, with each 1-percent decline saving our Nation about $500 billion. U.S. death rates from heart disease and stroke have declined more than 60 percent in the last half-century. Between 1997 and 2006, the death rate among adults with diabetes declined by 23 percent.

However, health advances aside—and they are paramount—the reduction of healthcare costs in the future may be one of the most significant contributions to society from medical research. As baby boomers age, the cost of healthcare will continue to increase. For example, a study led by economists at the RAND Corporation stated that the cost of dementia care is projected to double over the next 30 years, surpassing healthcare expenses for both heart disease and cancer. Without a way to prevent, cure, or effectively treat dementia, it will be difficult, if not impossible, to rein in costs. But science has confronted similar healthcare challenges in the past and prevailed. In the mid-20th century, economists predicted polio would cost taxpayers $100 billion a year to treat patients in "iron lung hotels." In the face of this challenge, medical research produced a solution to this devastating disease. Polio is now on the verge of being eradicated worldwide.

In the next few years as we confront difficult spending choices, I believe we must prioritize our Federal commitment to NIH. It is crucial that our next generation of biomedical researchers, the ones who will develop better and more cost-effective healthcare, remain in the scientific research field. Without adequate and sustained Federal support for medical research, trainees will be driven from the medical field or into the arms of our global competitors. Last year, China's Government pledged to increase basic research investment by 26 percent and will contribute more than $300 billion into biotechnology over the next 5 years. In the last 5 years, China's percentage of science and engineering degrees earned by university students was more than double those earned by U.S. students.

Without continued investment in the NIH we jeopardize our current scientific progress, risk losing a generation of scientists, and stunt our Nation's global competitiveness. This is not the time to waiver on America's commitment to the NIH and the health of all Americans.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you very much, Senator Moran.

And we welcome back again Dr. Francis Collins, the 16th Director of the National Institutes of Health, a physician and geneticist noted for discoveries of disease genes and his leadership of the Human Genome Project, of which he was the director from 1993 to

2008. Dr. Collins received a B.S. from the University of Virginia, his Ph.D. from Yale, and an M.D. from University of North Carolina at Chapel Hill.

Dr. Collins, your statement will be made part of the record in its entirety. And, again, the floor is yours. Please proceed as you so desire.

SUMMARY STATEMENT OF DR. FRANCIS S. COLLINS

Dr. COLLINS. Well, good afternoon, Mr. Chairman and members of the subcommittee. I'm very pleased to be here with my colleagues to present the President's budget request for the National Institutes of Health for fiscal year 2014.

This panel has a long history of supporting NIH's mission to seek fundamental knowledge and apply it in ways that enhance human health, lengthen life, and reduce suffering.

My sincere thanks to you, Mr. Chairman, for your strong commitment to supporting biomedical research over these years. NIH and millions of patients are grateful for that leadership.

But I'm here today to talk about the Administration's fiscal year 2014 budget request of $31.331 billion, which is a $471 million, or 1.5 percent, increase over fiscal year 2012. This budget request will enhance NIH's ability to support cutting-edge research and training of the scientific workforce, with the ultimate goal of speeding up development of new ways to improve human health.

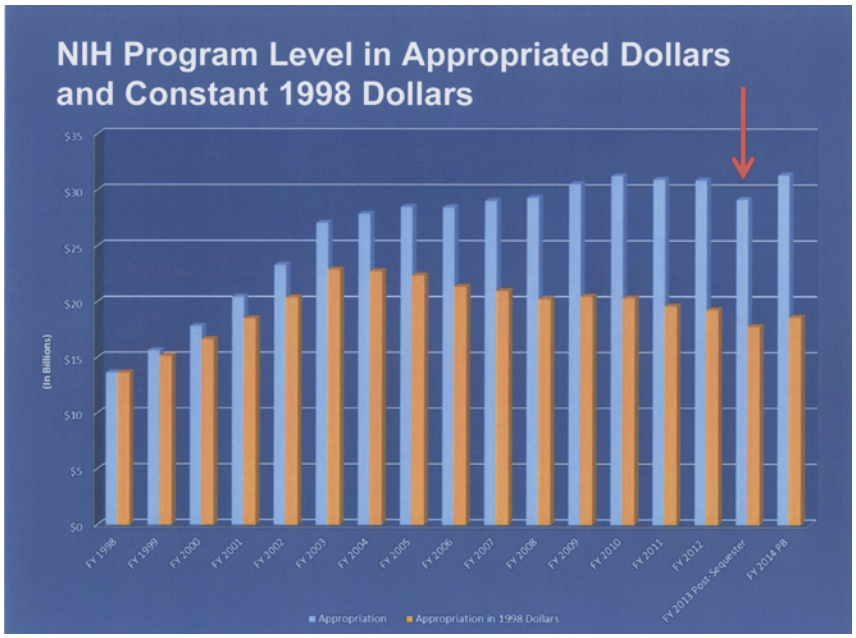
This request allocates resources to areas of extraordinary promise while allowing flexibility to pursue unplanned scientific opportunities and address unforeseen health needs.

But even with these tremendous scientific opportunities before us, and our hopes for your support in fiscal year 2014, we cannot ignore the current fiscal situation. As the chairman has just said, this is a perilous moment.

As you know, and despite this subcommittee's best efforts to avert it, sequestration took effect on March 27. Frankly, this has already dealt a devastating blow to NIH and to the entire biomedical research enterprise.

We're absorbing a $1.7 billion cut to our budget—and without action by this Congress, that will result, from the sequester, in a loss of $19 billion over the next 10 years.

NIH PURCHASING POWER



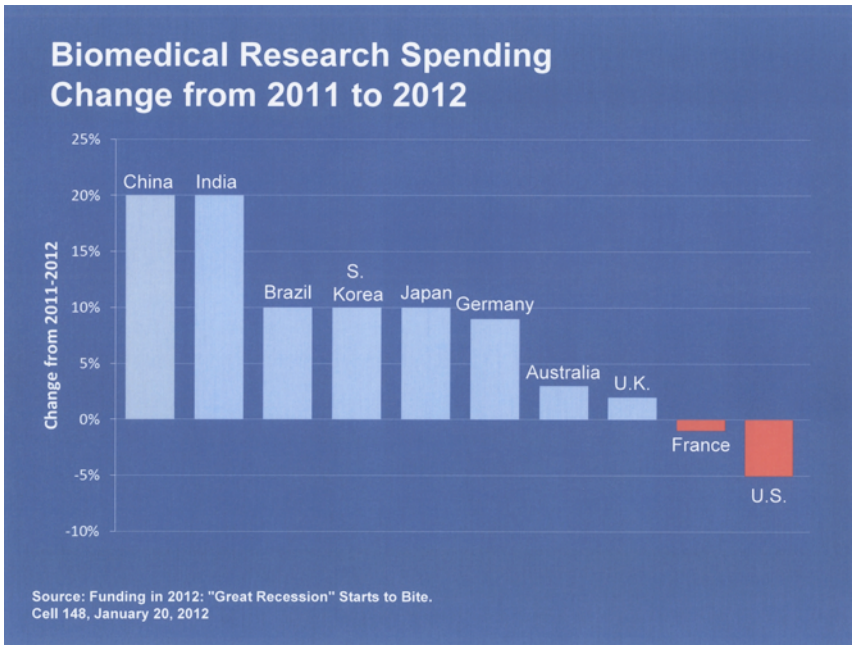
This graph that I'm showing you shows in blue the appropriated levels to NIH and the effects of inflation in orange. So including the sequester, which you can see identified by this red arrow, that leads to a significant downturn in fiscal year 2013, and which we hope will turn back up again with the President's budget proposal for 2014, almost 22 percent of the purchasing power for research has been lost versus 10 years ago, as you stated, Mr. Chairman.

The consequences are stark. Look back at 2003. At that point, as a direct result of the efforts of this subcommittee, NIH was supporting a total of 38,216 research project grants. Now, a decade later, with all the scientific opportunity in front of us, that number has fallen by more than 3,300 grants. And the drop is particularly severe in fiscal year 2013, where we'll be funding 700 fewer new and competing research project grants done in fiscal year 2012. Which of those grants might have led to the next big discovery in cancer research or launched a career of a promising young scientist? We will never know.

The paradox of my directorship at this time of unprecedented scientific opportunity, when we should be making progress by leaps and bounds towards curing human disease, is that our resources are suffering a historic downturn.

This cut in support in biomedical research in the U.S. is particularly troubling when one considers the investments being made in the rest of the world, as Senator Moran has referred to.

WORLDWIDE INVESTMENT IN BIOMEDICAL RESEARCH

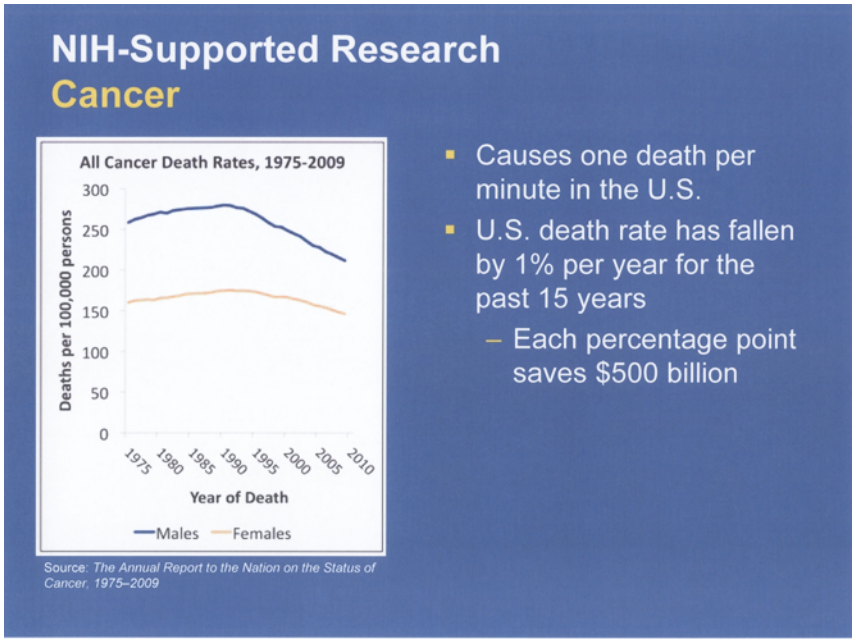


This bar graph is really quite striking, and I don't think anyone can look at it without being troubled by its significance. It shows the relative increases in support for biomedical research by countries around the globe. And you will notice the United States stands out on this graph in a very troubling way.

Mr. Chairman, I cannot gloss over the severity of this situation. The potential damage to scientific momentum, economic growth, and morale is profound.

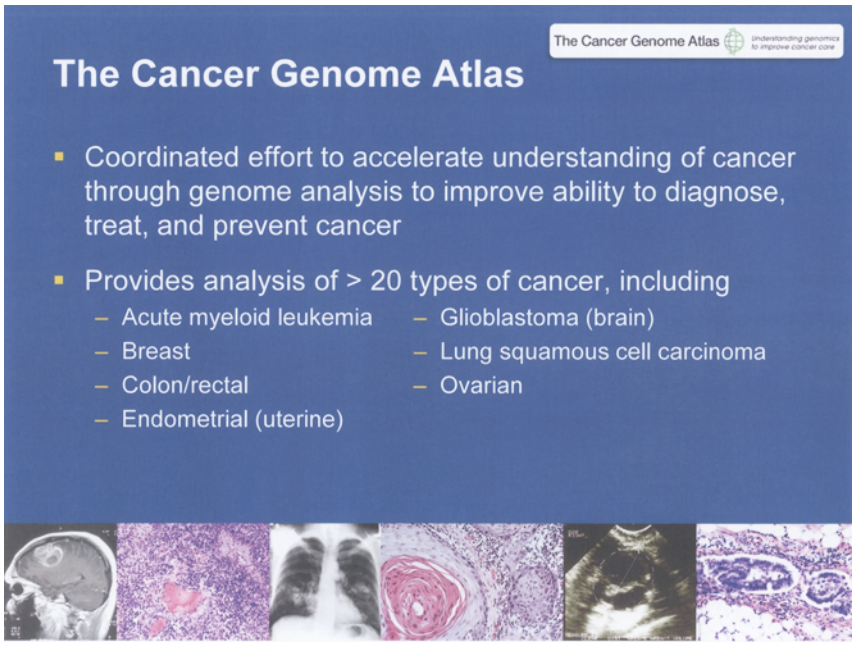
Despite these trying times, NIH has continued to pursue our mission and has been accelerating scientific discovery in several key areas, and I'd like to highlight a couple of those.

CANCER: DECREASE IN DEATH RATES



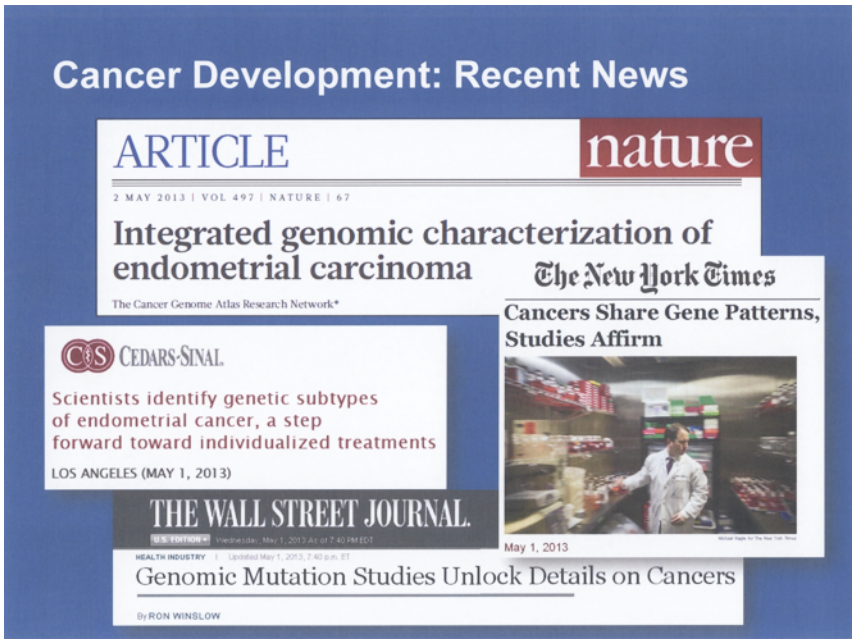
Let's consider cancer. One person dies from cancer every minute in the United States. NIH research has contributed to real progress with cancer death rates falling by 1 percent per year for the last 15 years, as already cited by Senator Moran. Economists estimate that each 1 percent drop is saving the U.S. $500 billion, making this an extremely good investment. But we are actually positioned to do much more.

THE CANCER GENOME ATLAS (TCGA)



The Cancer Genome Atlas, or TCGA, is a coordinated effort to accelerate our understanding of the molecular basis of cancer using dramatic advances in genome sequencing technologies to carry out comprehensive analysis of more than 20 types of cancer. By identifying the molecular changes in a cancer cell, as compared to a healthy cell of the same individual, we are gaining a better understanding of the driving forces behind the disease.

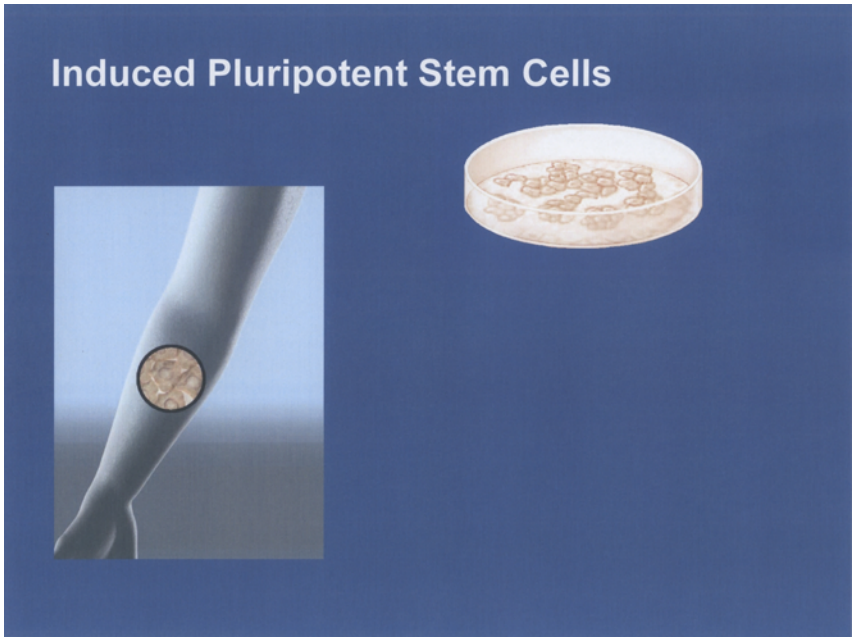
NIH-FUNDED RESEARCH MAJOR DEVELOPMENTS



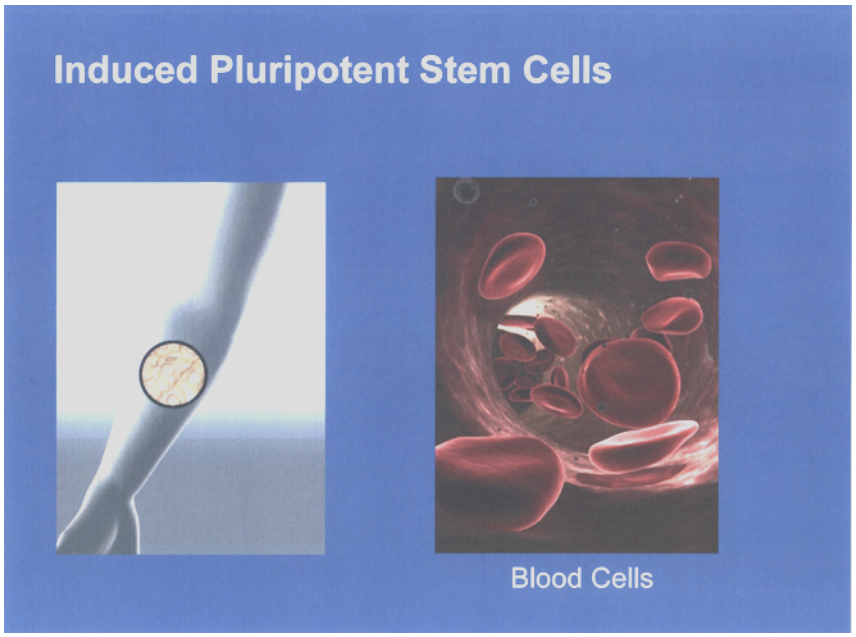
For example, very recently, NIH-funded researchers reported a major development. And in a study widely reported in the news media, they discovered that the genetic profile of a deadly form of uterine cancer closely resembles the profiles of the most lethal ovarian and breast cancers. This result has dramatic implications for prognosis and treatment.

And this breakthrough, and others like it, is leading to the identification of new therapies tailored to the patient's unique genetic profile that can empower personalized interventions, and precision medicine instead of one-size-fits-all chemotherapy.

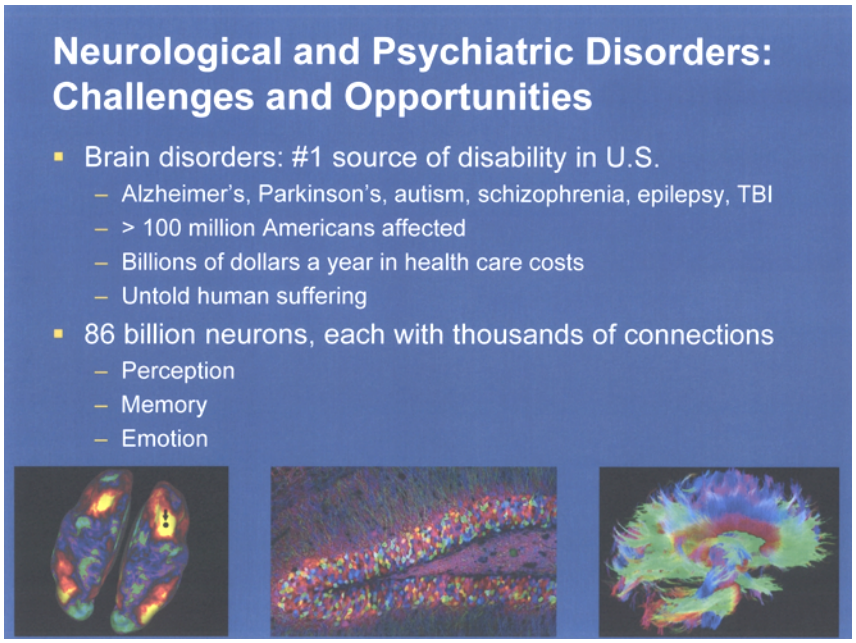
STEM CELL ADVANCEMENTS



Another example of how NIH-supported research is advancing biomedical discovery is in the area of stem cells. Induced pluripotent stem cells, also known as iPS cells, are revolutionizing the way we study disease. iPS cells are mature cells typically derived from a patient's skin that researchers can reprogram back to an immature state. These cells can then be programmed into a wide variety of cell types, including liver cells, neurons, or blood cells.



This means we can start with a skin biopsy from a patient and then re-create that same individual's disease in a Petri dish. We can learn molecular details about the disease and even test potential drugs to see if they are likely to be safe and effective. It may one day even be possible to use these cells therapeutically. You can imagine how this might work, for instance, for a disease of the blood, such as sickle cell anemia. But we're not stopping there.



I'd like now to focus on a landmark new scientific endeavor that we're planning for fiscal year 2014. Neurological and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, autism, schizophrenia, epilepsy, and traumatic brain injury inflict a tremendous toll on society yet their underlying pathology has remained largely unknown due to the enormous complexity of the human brain.

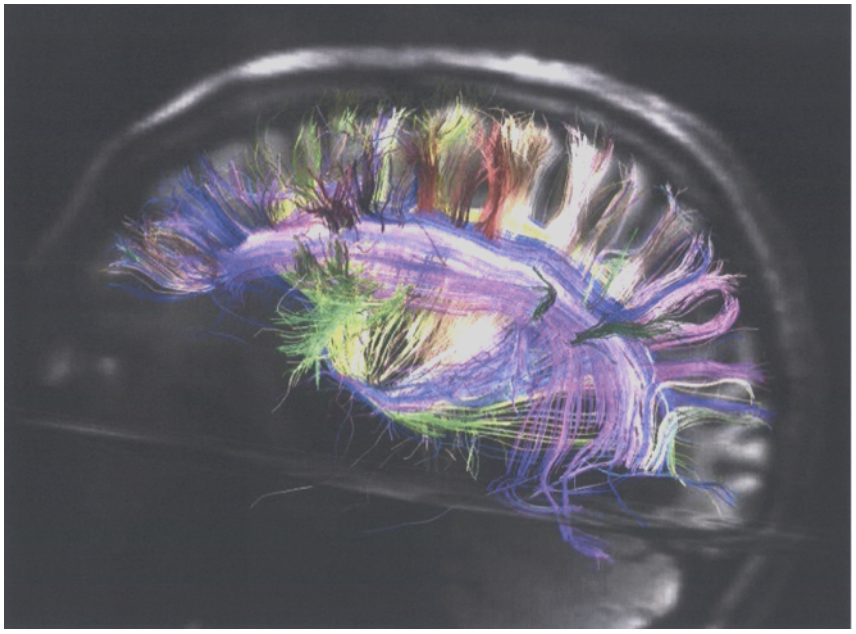
This complexity, built on 86 billion neurons—that's what you got up there—each with thousands of connections was once thought to be beyond the reach of scientific understanding. Today, however, tremendous strides in neuroscience have created new opportunities for unlocking these mysteries and have placed us in the position of proposing a truly bold new initiative.

And so in fiscal year 2014, NIH will begin its support of the Brain Research through Advancing Innovative Neurotechnologies, B–R–A–I–N, the BRAIN Initiative. The goal of this initiative is to accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact, all at the speed of thought.

To do that, we need to be able to record signals in much greater numbers of brain cells at a much more rapid pace than is currently possible. And while recent innovations like functional magnetic resonance imaging (MRI) have contributed substantially to our expanding knowledge of the brain, significant breakthroughs on how we treat neurological and psychiatric disease will require a new generation of tools.

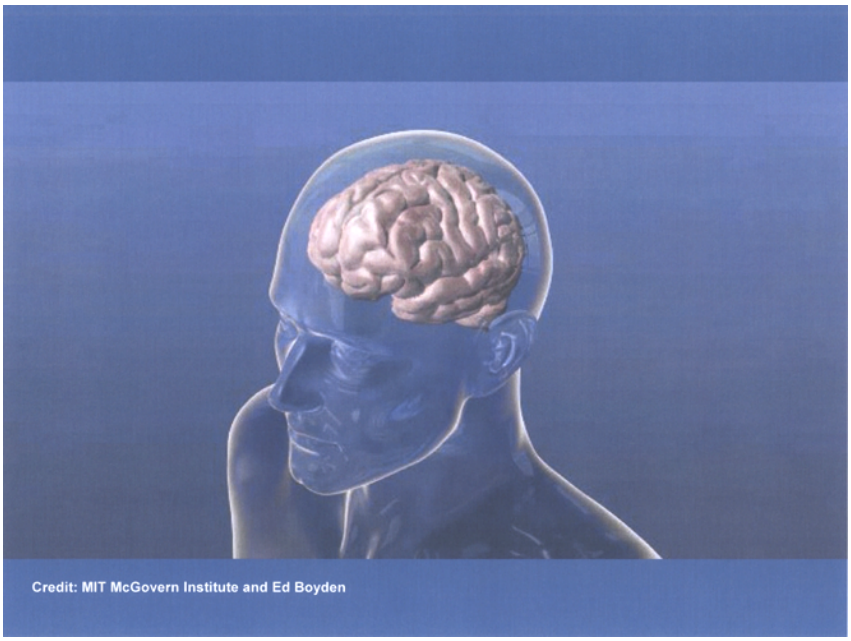
By measuring activity at the scale of circuits and networks in living organisms, we can begin to translate data into models that will decode sensory experience, motor activity, and potentially even memory, emotion, and thought. So how do we set about doing this?

HUMAN CONNECTOME PROJECT



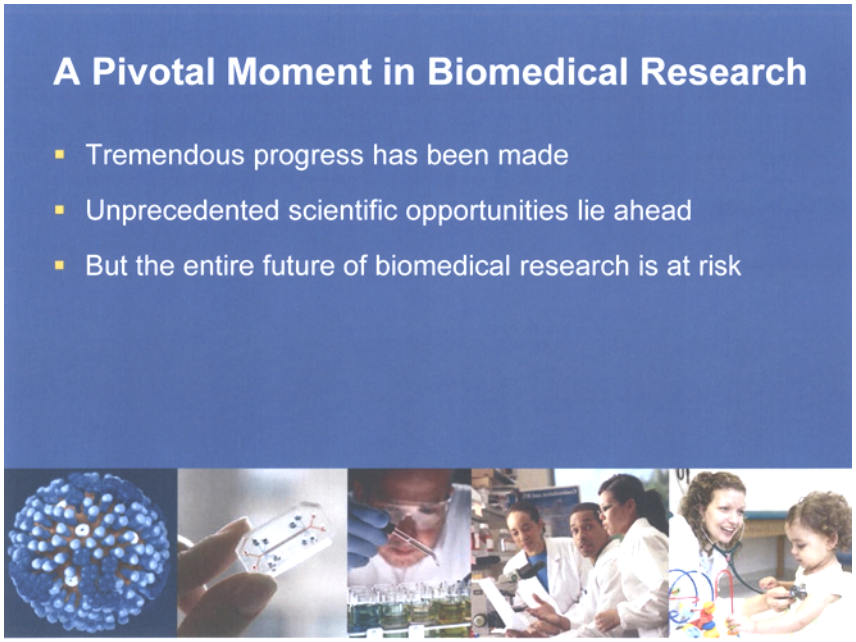
Another major NIH initiative has already laid the groundwork for mapping the human brain, the Human Connectome Project. This is an image, a noninvasive image, of a healthy human being, using a new kind of MRI. This connectome depends upon a dramatic set of advances in MRI scanning, giving this 3–D picture of a wiring diagram of nerve cells in your brain.

Interestingly, this proves that you are more than just your deoxyribonucleic acid (DNA). Environmental factors and life experiences work in concert with genetics to create your unique neural connections. And this is where the BRAIN Initiative comes in. It is designed to develop technologies that are capable of recording the activity of hundreds of thousands of neurons in real time, allowing us to determine the way in which brain circuits actually function.



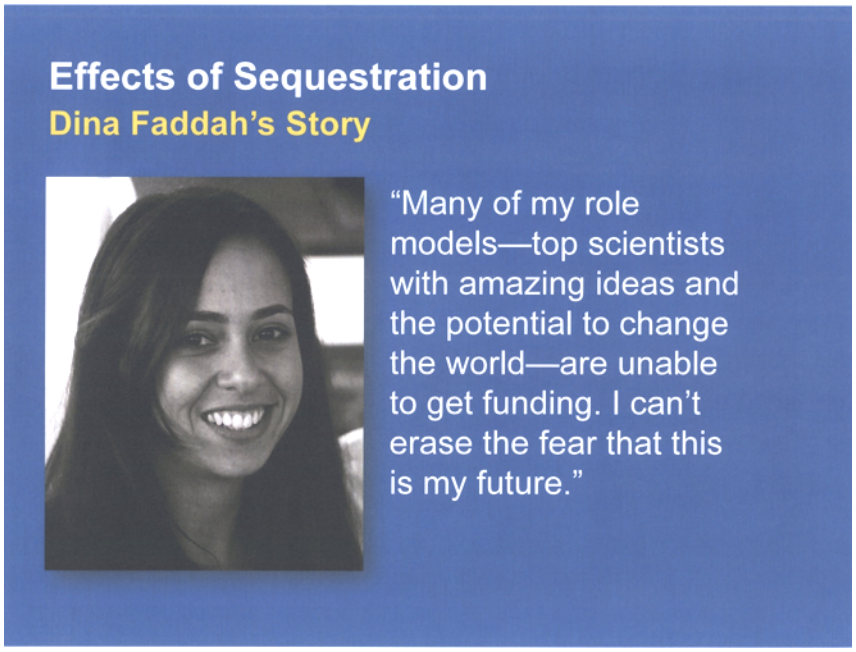
The BRAIN Initiative is ambitious, and the details of a plan that will stretch over a decade or more are being worked out. But we must begin now. The BRAIN Initiative will provide a better understanding of the roots of human neurological disorders, revolutionize the field of neuroscience, and set the stage for major advances in diseases that will catalyze the development of new treatments and cures.

DR. COLLINS' SUMMARY



So, to sum up, today I've told you about the tremendous scientific progress we've already made and a few of the many fantastic opportunities that lie on the horizon. However, I need to drive home, again, the impact of sequestration.

Let me close by putting a human face on exactly who is at risk during these trying fiscal times.



I recently met with Dina, one of my former superstar students, who spent 2 years working in my lab at NIH before deciding to go on to graduate school. She's now finishing her Ph.D. at MIT and has done spectacular work in developmental biology. But she sees what is happening to biomedical research in the United States, and she is sufficiently worried about her own future to begin to consider other options quite seriously.

In fact, many of her contemporaries have begun looking for options outside of science or outside of this country. She wrote me these words after our recent meeting: "Many of my role models—top scientists with amazing ideas and the potential to change the world—are unable to get funding. I can't erase the fear that this is my future."

This is a defining moment. My fear is that we're putting an entire generation of U.S. scientists at risk. And if they go away, they won't come back.

Sequestration is compromising the future of biomedical research and slowing improvement in the health of all Americans.

So, thank you, Mr. Chairman. I look forward to answering any questions you and this committee may have.

[The statements follows:]

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

Good afternoon, 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 Insti-

tutes of Health (NIH). Accompanying me today are: Anthony S. Fauci, M.D., Director of the National Institute of Allergy and Infectious Diseases; Gary H. Gibbons, M.D., Director of the National Heart, Lung, and Blood Institute; Richard J. Hodes, M.D., Director of the National Institute on Aging; Story C. Landis, Ph.D., Director of the National Institute for Neurological Disorders and Stroke; and Harold E. Varmus, M.D., Director of the National Cancer Institute.

It is an honor to appear before you today to present the Administration's fiscal year 2014 budget request for the NIH.

NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance human health, lengthen life, and reduce illness and disability. I can report to you that NIH leadership, employees, and grantees continue to believe passionately in our mission.

NIH has been advancing our understanding of health and disease for more than a century, and scientific and technological breakthroughs generated by NIH-supported research are behind much of the gains this country has enjoyed in public health. For example, deaths from heart attack have fallen by more than 60 percent over the past 40 years; deaths from stroke by more than 70 percent. HIV/AIDS treatment and prevention may now enable us to envision the first AIDS-free generation since this virus emerged more than 30 years ago. More than 90 percent of children diagnosed today with the most common form of childhood leukemia will survive. NIH research has given us vaccines for cervical cancer, influenza, and meningitis. We can look forward to a future in which advanced prevention and treatment strategies such as these allow everyone to have a much better chance of living a long and healthy life.

I would like to begin today by highlighting just a few areas in which NIH-supported research is opening up extraordinary new opportunities to improve the health of the American public.

Let's consider cancer. One person dies from cancer every minute in the United States—that equates to 1,500 deaths every day, the equivalent of five crashing jumbo jets.[1] NIH research has contributed to real progress, with cancer death rates falling by 1 percent per year for the past 15 years—but we aim to do much more. With the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) as leads, NIH established The Cancer Genome Atlas (TCGA) as a coordinated effort to accelerate our understanding of the molecular basis of cancer, using dramatic advances in genome sequencing technologies to carry out comprehensive genomic analysis of more than 20 types of cancer. By identifying the molecular changes in a cancer cell as compared to a healthy cell of the same individual, we are gaining a better understanding of the driving forces behind the disease. That is leading to identification of new drug targets, as well as of subsets of disease with different responses to therapy that can empower personalized interventions instead of one-size-fits-all chemotherapy. As an example, a TCGA research network of investigators recently identified promising new therapeutic targets in squamous cell carcinoma of the lung, the second most common form of lung cancer, including three families of enzymes that act as molecular switches.[2] These findings lay the foundation for the development and implementation of advanced diagnostics and treatments for squamous cell cancer. Moreover, they underscore the value and promise of our Nation's investment in TCGA.

Another new and exciting area of basic research is the Human Microbiome Project. Microbes inhabit many parts of the human body and have often had a bad reputation for causing sickness. But more often than not, they actually contribute to the health of their human hosts. In a 5-year endeavor supported by the NIH Common Fund, 200 scientists at 80 institutions sequenced the genomes of bacteria from multiple body sites of 250 individuals, with striking results. The research showed that certain communities of bacteria help keep people healthy, whereas others appear to make people more susceptible to disease.[3] When the bacterial population in the intestinal tract gets disrupted, chronic conditions such as obesity can result; this new understanding may provide us with novel ways to address this serious health threat. An unexpected result from another NIH-funded study was that poor diet is not the only contributor to malnutrition. In fact, a bad assortment of microbes in the gut can conspire with a nutrient deficient diet to lead to severe malnutrition.[4]

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[1] http://cancergenome.nih.gov/PublishedContent/Files/pdfs/1.1.0__CancerGenomics__TCGA-Genomics-Brochure-508.pdf.

[2] http://www.nature.com/nature/journal/v489/n7417/pdf/nature11404.pdf.

[3] http://www.nature.com/nature/journal/v486/n7402/pdf/nature11209.pdf.

[4] http://www.sciencemag.org/content/339/6119/548.full.pdf.

A final example I want to provide of how NIH-supported research is accelerating scientific discovery is in the area of stem cells. Induced pluripotent stem (iPS) cell technology is revolutionizing the way we study disease, and holds the promise of dramatic advances in treatment. iPS cells are patient-derived cells, typically from skin, that scientists can reprogram back to an embryonic stem cell-like state. These cells can then be induced to turn on specific sets of genes to differentiate into a variety of cell types, including blood cells, liver cells, or neurons. This means researchers can re-create a patient's disease in a dish and screen drug compounds against the cells—rather than the patient—to determine drug toxicity and efficacy. But it's also possible that these cells could be used therapeutically, especially if an individual's genetic misspellings could be corrected in their own iPS cells, and then programmed and delivered to a tissue where they are sorely needed. Recent NIH-funded studies have developed copy-editing enzymes that are making it faster, easier, and cheaper to correct genetic typos. In 2011, researchers used a specially engineered copy-editing enzyme to find and correct the mutation that causes sickle cell anemia using iPS cells derived from a patient with the disease.[5] Two very recent, groundbreaking discoveries along this same avenue are the development of the next generation methodology of "find and replace" enzymes that are making it much simpler to copy-edit the genome.[6] [7]

While these exciting findings have led to a much deeper understanding of health and human disease, much more work needs to be done in order to move these strategies and others like them out of the lab and into the clinic—and to do so as quickly as possible. To this end, the Administration's fiscal year 2014 budget request for the NIH is $31.331 billion, $471 million above the fiscal year 2012 level. This budget request reflects the President's and the Secretary's commitment to improving the health of the Nation and to maintaining our Nation's leadership in the life sciences. The request highlights investments in innovative research that will advance fundamental knowledge and speed the development of new therapies, diagnostics, and preventive measures to improve public health.

The fiscal year 2014 budget request, a 1.5-percent increase over fiscal year 2012, will enhance NIH's ability to support cutting-edge research and training of the scientific workforce. Within the Administration's fiscal year 2014 budget, we will continue to increase Research Project Grants (RPGs), NIH's funding mechanism for investigator-initiated research. NIH expects to support 10,269 competing RPGs in fiscal year 2014, an increase of 1,283 over fiscal year 2012 levels. For fiscal year 2014, NIH anticipates funding a total of 36,610 RPGs. The budget request allocates resources to areas of the most extraordinary promise for biomedical research, while maintaining the flexibility to pursue unplanned scientific opportunities and address unforeseen health needs.

A major initiative for NIH in fiscal year 2014 will be in the area of Alzheimer's disease research. As many as 5.1 million Americans suffer this irreversible, progressive, and devastating brain disease that slowly destroys cognitive functions including memory and the ability to reason and think.[8] At the same time, millions of American families struggle with the physical, emotional, and financial costs of caring for a loved one with Alzheimer's. A recently published NIH-supported study found the costs of caring for people with dementia in the United States in 2010 ranged from $157 billion to $215 billion.[9] This disease is not just a burden on our health, but also a burden on our economy.

NIH, with the National Institute on Aging (NIA) taking the lead, currently supports a number of studies aimed at understanding, diagnosing, preventing, and treating Alzheimer's disease. In fiscal year 2014, NIA would plan to award a total of 591 new and competing RPGs, an increase of 277 from fiscal year 2012. This includes an $80 million increase for Alzheimer's research.

A seminal finding that has recently generated a lot of excitement is the discovery that the protein, tau, which appears to be in part responsible for the cognitive decline in Alzheimer's patients, spreads from neuron to neuron like an infection.[10] This means that if researchers could find a way to prevent cell-to-cell transmission, perhaps by blocking tau with an antibody, the disease process could be halted. There is also growing evidence that successful treatment of Alzheimer's disease needs to happen very early in the course of the disease, perhaps even before any symptoms have appeared at all. This kind of Alzheimer's disease prevention is at

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[5] http://onlinelibrary.wiley.com/doi/10.1002/stem.718/pdf.
[6] http://www.sciencemag.org/content/326/5959/1501.full.pdf.
[7] http://www.sciencemag.org/content/339/6121/819.full.pdf.
[8] http://www.nia.nih.gov/alzheimers/topics/alzheimers-basics.
[9] http://www.nejm.org/doi/pdf/10.1056/NEJMsa1204629.
[10] http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0031302.

the heart of new clinical trials being conducted by scientists at the Dominant Inherited Alzheimer's Network (DIAN), a NIA-funded international research partnership. One of the investigational drugs being tested is a monoclonal antibody that binds to certain forms of amyloid beta, a main constituent of the signature plaques in Alzheimer's disease. Trying to prevent Alzheimer's symptoms from ever occurring in individuals at very high genetic risk is a new strategy—one that we are eager to pursue in order to determine if early intervention can influence this terrible disease.

With advancing scientific and technological capabilities, such as genome sequencing machines and high resolution medical imagers, biomedical researchers are generating huge amounts of data at an unprecedented pace. The need to integrate and analyze massively complex datasets is referred to as the Big Data challenge—a challenge that we must overcome to gain a deeper understanding of disease and develop the next generation of therapeutic targets.

Managing Big Data is a critical part of translating scientific discoveries into clinical applications. To address this challenge, NIH is developing the Big Data to Knowledge (BD2K) program, which will be launched in fiscal year 2014. BD2K will support four programmatic efforts: (1) facilitate the broad use and sharing of large, complex biomedical data sets through the development of policies, resources and standards; (2) develop and disseminate new analytical methods and software; (3) enhance training of data scientists, computer engineers, and bioinformaticians; and (4) establish Centers of Excellence to develop generalizable approaches that address important problems in biomedical analytics, computational biology, and medical informatics. In fiscal year 2014, NIH will invest at least $40 million in the BD2K program through the Common Fund, and each Big Data Center of Excellence will be funded at $2 million to $5 million per year for 3 to 5 years. As Big Data challenges in biomedical research are shared with other areas of scientific research such as energy and space research, BD2K will also require effective collaboration and coordination with other Government agencies tackling similar challenges, including the National Science Foundation and the Department of Energy, as well as privately funded efforts. With the proper investments and efforts, we will overcome the challenges associated with Big Data in order to accelerate the translation of bench to bedside applications.

Another exciting new initiative I would like to tell you about is NIH's efforts to recruit and retain a diverse pool of scientific talent and creativity. NIH is strongly committed to maintaining a diverse biomedical research workforce and has supported programs to enhance the diversity of our workforce for more than 30 years in order to achieve this goal. While progress has been made in some areas, more work needs to be done. The centerpiece of the newest initiative is the BUilding Infrastructure Leading to Diversity (BUILD) Program that is designed to provide relatively under-resourced institutions with the opportunity to provide a series of rigorous, mentored research experiences to their students, many of whom are from backgrounds underrepresented in biomedical research, with the goal of facilitating entry of a more diverse pool of students into graduate programs for biomedical research.

I want to emphasize that while all of these ambitious new scientific endeavors provide unprecedented promise for advancing human health, we cannot ignore the impact the sequester is having on groundbreaking medical research. The fiscal year 2013 reduction of $1.6 billion, or 5.0 percent, is having a substantial impact on the scientific community. If the Budget Control Act-imposed caps on discretionary programs continue, and NIH funding is reduced proportionally over the next 10 years, funding will decline by about $19 billion. The consequences will be harmful to scientific progress and to American leadership in science. NIH-funded investigators are already feeling the effects as Institutes and Centers are forced to fund a lower percentage of grant applications. In fiscal year 2012, we funded 8,986 competing RPGs. In fiscal year 2013, our projection is 8,283. This trend is also reflected in our total research portfolio—we expect to fund 34,902 RPGs this year compared to 36,259 in fiscal year 2012. With this new reality, more and more investigators will be unable to pursue the bold ideas that NIH has traditionally supported.

NIH plays a significant role in the U.S. economy by advancing scientific products and technologies that help maintain our Nation's role as a global innovation leader.[11] At a time when global competition in the life sciences is intensifying, the American economy cannot afford to lose ground in scientific efforts that promote human health. Countries such as China and India are increasingly investing resources into biomedical science and technology. According to the Organization for Economic Cooperation and Development (OECD), in 2008, including both public and

[11] http://www.unitedformedicalresearch.com/wp-content/uploads/2013/02/UMR__Impact__of__Sequestration__2013.pdf.

private sources, the U.S. invested 2.8 percent of its GDP in research and development (R&D)—less than Israel, Japan, Korea, Sweden, and Switzerland. Moreover, the U.S. ranks only eighth in R&D as a share of GDP among countries in the OECD.[12] China has made policy changes to invest heavily in the life sciences industry, moving them closer to becoming a world leader in science and technology by the end of the decade.[13] Over the past decade, Singapore has also pursued a prominent role as a global leader in the life sciences. For example, their pharmaceutical industry R&D funding was five times greater than that of the U.S. in 2009, on a share of GDP basis. Despite these factors, the United States is by far the largest R&D performer globally, contributing $402 billion in 2009, accounting for about 31 percent of the global total.[14]

But let me close on a more positive note. I began today by telling you about some exciting new initiatives NIH is planning for fiscal year 2014. Now I want to tell you about our boldest new scientific endeavor—one that we are all very excited about.

Neurological and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, autism, schizophrenia, and traumatic brain injury inflict a tremendous toll on society, yet their underlying pathologies remain unknown due to the great complexity of the human brain. This complexity was once thought to be beyond the reach of scientific understanding. Today, however, tremendous strides in neuroscience have brought forward remarkable new opportunities for unlocking these mysteries.

Indeed, neuroscience has made some extraordinary progress in recent years. For example, a group of NIH-supported researchers has developed a sophisticated neural interface that enables paralyzed people to move a robotic arm, using just their thoughts. Using this robotic arm system, 58-year-old Cathy Hutchinson recently was able to take a sip of coffee on her own for the first time since she'd been paralyzed more than 14 years earlier. A truly remarkable moment—but just a beginning, because we need a lot more of these moments for a whole lot more people.

In fiscal year 2014, NIH will begin its support of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, in order to develop a deeper understanding of brain function through the creation of new tools capable of examining the activity of millions of nerve cells, networks, and pathways in real time. By measuring activity at the scale of circuits and networks in living organisms, we can begin to translate data into models that will decode sensory experience, motor planning, and, potentially, even memory, emotion, and thought. NIH is embracing a collaborative approach in tackling this challenge, working with researchers from across the country, industry, foundations, and other Government agencies including the Defense Advanced Research Projects Agency and the National Science Foundation. In fiscal year 2014, NIH will invest $40 million in this initiative to leverage investment from a number of other sources, including private sector and leading philanthropies. We believe that successful completion of the BRAIN Initiative will revolutionize the field of neuroscience and set the stage for major advances in diseases such as Alzheimer's, Parkinson's, autism, schizophrenia, depression, and epilepsy.

Granted, this is a very ambitious goal. But we at NIH have heard and overcome such skepticism before. Take the example of the Human Genome Project, which I had the privilege to lead. In its earliest days, back in the late 1980s, many questioned the wisdom of that proposal to sequence the 3 billion letters in the human genetic blueprint. Nearly everyone in the research community agreed that it would be fantastic to have a full readout of the human DNA instruction book. But skeptics argued that it could not be done because the tools and technologies didn't exist. In fact, they were right—we didn't have the necessary technologies. But, the opportunity for dramatic progress in genetics inspired a remarkable series of technical innovations. These tools enabled the Human Genome Project to be successfully completed in April 2003, ahead of schedule and under budget. Like the Human Genome Project, we envision the BRAIN Initiative will create data, tools, and technologies that will speed the efforts of many different types of researchers all around the world. Though this program will need to extend over many years, and we must be careful not to overpromise immediate medical benefits, BRAIN will eventually lead to scientific advances that will catalyze development of new treatments and cures.

I have provided you today with a brief overview of NIH's past successes and continuing commitment to basic and translational science, as well as a glimpse into the critical role that NIH plays in our domestic and global economies. We have never

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[12] http://www.itif.org/publications/winning-race-2012-memos-science-and-technology.

[13] http://www.itif.org/publications/leadership-decline-assessing-us-international-competitiveness-biomedical-research.

[14] http://www.nsf.gov/statistics/seind12/c4/c4s8.htm.

witnessed a time of greater promise for advances in medicine than right now. With your support, the future of medicine will be very bright.

This concludes my testimony, Mr. Chairman.

PREPARED STATEMENT OF ANTHONY S. FAUCI, M.D.

Mr. Chairman and members of the committee: I am pleased to present the President's budget request for the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The fiscal year 2014 NIAID budget of $4,578,813,000 includes an increase of $96,444,000 over the comparable fiscal year 2012 level of $4,482,369,000.

NIAID conducts basic and clinical research with the ultimate goal of improving human health through the development of diagnostics, therapeutics, and vaccines for infectious diseases; and to increase our understanding of the immune system, how it protects us from infection and disease, and its role in immune-mediated diseases. NIAID also addresses the scientific challenges that arise from emerging and re-emerging infectious diseases, including influenza, HIV/AIDS, tuberculosis, and malaria.

INFECTIOUS DISEASES RESEARCH

HIV/AIDS.—Through more than 30 years of supporting and conducting basic and clinical research, NIAID has provided the scientific foundation for groundbreaking interventions and strategies to treat and prevent HIV/AIDS, including combination antiretroviral therapy (ART), pre-exposure prophylaxis (PrEP), medical male circumcision, prevention of mother-to-child transmission (PMTCT), microbicides, and antiretroviral treatment as prevention. It is an exciting time in the domestic and global fight against HIV/AIDS, and NIAID continues to support research critical to a goal now within our reach: an AIDS-free generation. The NIAID-funded HPTN–052 clinical trial—the "Science" magazine 2011 Breakthrough of the Year—conclusively demonstrated that treatment of the HIV-infected person in a stable heterosexual relationship with an uninfected partner dramatically reduces the likelihood of transmitting HIV to the uninfected partner. Recently, based upon results of the NIAID-funded iPrEx study and other research, the Food and Drug Administration (FDA) approved the ART combination drug Truvada® as a prevention tool for uninfected adults at high risk of acquiring HIV. Ongoing NIAID studies of PrEP, microbicides, and PMTCT are exploring new strategies to limit HIV transmission in various populations; one study (TLC-Plus) is evaluating the feasibility of a community-level "testing, link to care, and treatment" strategy; and the new population-based ART study (PopART) will determine the effects of universal testing and immediate ART on HIV transmission.

NIAID continues its longstanding efforts to develop an effective HIV vaccine. NIAID is currently investigating the reasons for the modest efficacy (31 percent protection) of the HIV vaccine candidates used in the RV–144 clinical trial conducted in Thailand several years ago, and will seek to achieve significantly better results with future vaccine candidates. In this regard, NIAID has funded two new HIV vaccine initiatives and also is moving into Phase I clinical trials to determine if passively transferred neutralizing antibodies can protect against HIV infection.

Tuberculosis and Malaria.—Drug-resistant forms of tuberculosis (TB) are emerging worldwide, and co-infection with TB and HIV is a major cause of morbidity and mortality in the developing world. NIAID is helping to bring TB research into the 21st century by applying microbial genomic sequencing technologies, investing in the basic science underlying point-of-care diagnostics, supporting research to develop vaccine candidates, and engaging in public-private partnerships for drug development. These efforts are bearing fruit: NIAID researchers showed the potential of linezolid (originally developed for staphyloccocal infections) as a treatment for extensively drug-resistant TB, and FDA recently approved the first new TB drug (bedaquiline) in decades.

NIAID continues its work to combat malaria. To counter the emerging resistance to artemesinin, a first-line malaria drug, NIAID scientists have identified a region in the genome of the parasite linked to artemesinin resistance. NIAID is pursuing its promising efforts to develop candidate malaria vaccines, including studies conducted at the NIH Clinical Center.

Other Infectious Diseases of Domestic and Global Health Importance.—Events in the news remind us almost on a daily basis of the global threat of emerging and re-emerging infectious diseases. Paramount among these are seasonal influenza and potential pandemic influenza threats, such as the H7N9 influenza emerging in China. NIAID conducts research on the pathogenesis and transmissibility of influ-

enza, and the emergence of epidemics and pandemics, with the goal of furthering the development of influenza diagnostics, therapeutics, and vaccines. We have made significant strides toward developing a universal influenza vaccine, which would obviate the need for annual influenza vaccination and enhance our ability to respond to the emergence of influenza pandemics. Though it will be years before this goal is achieved, NIAID grantees and scientists, including those at NIAID's Vaccine Research Center, have demonstrated success in animal models, and have begun Phase I trials in humans. In addition, the NIAID Human Immunology Project Consortium is characterizing human immune responses to improve vaccines and immunotherapeutics for a variety of infectious diseases, including influenza.

NIAID scientists have developed an animal model to study the novel coronavirus recently identified in Saudi Arabia, and to evaluate potential treatments and vaccines. They have shown recently that a combination of two antiviral drugs, ribavirin and interferon, can inhibit replication of the virus in cell culture.

Common microbial infections are increasingly becoming resistant to the drugs generally used to treat them. Methicillin-resistant "Staphyloccus aureus" (MRSA) has been a longstanding problem. Of particular concern is the recent emergence of other antibiotic-resistant organisms such as the carbapenem-resistant Enterobacteriaceae (CRE) including "Klebsiella pneumoniae". To address the challenge of antimicrobial resistance, NIAID continues its efforts in the development and testing of vaccines to prevent these infections, and in the evaluation of new and repurposed drugs to treat antimicrobial-resistant organisms. This year, NIAID will establish a leadership group for a national network to conduct clinical research on antibacterial resistance.

We are witnessing rapid changes in the treatment of hepatitis C virus (HCV), a major cause of chronic liver disease and a common co-infection with HIV. Promising new HCV protease inhibitor drugs recently approved by FDA were developed with the help of NIAID and other NIH Institutes. NIAID also is collaborating with industry to develop new HCV therapeutics and vaccines, and to test approved drugs in individuals with HCV/HIV co-infection.

NIAID biodefense research continues to build on our fundamental understanding of the biology of and immune response to microbes. Recent successes include FDA approval of a monoclonal antibody to treat anthrax and progress on vaccines against Ebola and other hemorrhagic fever viruses. NIAID biodefense research also addresses the global threat of emerging and re-emerging diseases, including the development of vaccines for dengue fever and animal models to study West Nile virus.

RESEARCH ON IMMUNOLOGY AND IMMUNE-MEDIATED DISORDERS

NIAID remains committed to basic and clinical research on the immune system and immune-mediated diseases, including the development and testing of adjuvants to enhance the immune response to vaccination. NIAID also supports groundbreaking studies in the treatment of food allergy, a significant concern for many Americans. Recently, NIAID-funded scientists found that oral egg immunotherapy can reduce and even eliminate allergic responses for extended periods in certain children. Similarly promising results showed that peanut immunotherapy given under the tongue can reduce the allergic response in adolescents and adults.

CONCLUSION

NIAID conducts critical research on infectious and immune-mediated diseases that ultimately will enable interventions to improve health domestically and worldwide. Understanding and developing countermeasures against microbes that threaten our public health is central to NIAID's mission. NIAID will continue to fund meritorious basic and clinical research with the ultimate goal of translating these discoveries into global public health benefits.

PREPARED STATEMENT OF GARY H. GIBBONS, M.D.

Mr. Chairman and distinguished 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 2014 budget of $3,098,508,000 includes an increase of $25,206,000 over the comparable fiscal year 2012 level of $3,073,302,000.

NHLBI leads research and education programs to discover and apply knowledge to improve health by preventing and treating heart, lung, and blood diseases. It is a privilege to serve as NHLBI Director in this time of unprecedented opportunity

in biomedical research. Today, I will discuss new opportunities to reduce health disparities, advance understanding of complex chronic diseases, and enhance clinical research.

HEALTH DISPARITIES RESEARCH

The NHLBI portfolio includes studies of many diseases that impose strikingly disparate burdens on Americans from different walks of life. Understanding and alleviating health disparities has been a passion of mine throughout my career, and I am honored to lead an Institute with such a longstanding commitment to supporting work in that area. Many of you are familiar with the NHLBI's large epidemiological studies that focus on minority populations, including the Jackson Heart Study in African Americans, the Hispanic Community Health Study, the Multi-Ethnic Study of Atherosclerosis, which includes a sizeable cohort of Asian Americans, and the Strong Heart study in American Indians. Our recent investments in genotyping of diverse cohorts promise to shed critical light on biological differences in disease susceptibility as well as the interactions between genes and environment as determinants of health among all Americans. We also have an outstanding record of including substantial numbers of minorities in our clinical research, particularly in studies of high blood pressure, which appears with great frequency and often devastating complications in African Americans.

Efforts to date have yielded progress that has benefited most people to some extent but, unfortunately, has done little to close the gaps that persist between the healthiest and least healthy segments of society. Because health disparities are complex and are clearly influenced not only by genetics but also by factors such as family, social community, and physical environment, we believe that they offer an excellent model for a new "systems" approach to our research strategy. Until recently scientists have had to consider such factors separately; for instance, one researcher might look at basic biological pathways or genetic factors, while another examines lifestyle choices and a third considers socioeconomic influences. This piecemeal approach provides a limited view of how disease occurs and, more important, how it can be prevented or managed effectively. To revolutionize our understanding of health and disease, we are now developing and exploiting new tools that enable consideration of many factors—biological, behavioral, environmental—together in a holistic way. That, I believe, is the path to future progress in preventing and preempting chronic heart, lung, and blood disorders. If we can develop the "systems" research model for health disparities research we can transform both science and medicine by applying it more broadly to other public health needs.

A NEW PARADIGM FOR UNDERSTANDING COMPLEX DISEASES

Let me give you one example of recent findings that highlight the value of a cross-disciplinary approach. We have known for decades that the foods we eat influence our risk of developing cardiovascular disease (CVD). Observational studies have taught us the value of so-called heart-healthy diets that emphasize fruits, vegetables, whole grains, fish, and "good" fats such as olive oil. Nevertheless, controversies persist about the potential harmful effects of red meat consumption. Scientists still don't know why certain foods increase or reduce the risk of CVD.

Recently, a provocative series of NHLBI-funded studies provided some important new insights into the potential link between red meat consumption and atherosclerotic CVD. Researchers have shown that the bacteria that reside in our guts and metabolize L-carnitine, a substance found in red meat, may be an important culprit behind CVD. This interaction between diet and gut microbes leads to the production of TMAO (trimethylamine-N-oxide), an organic compound that circulates in the blood and promotes the "clogging of arteries" by inhibiting the removal of cholesterol from atherosclerotic plaque.

This and other work is dramatically enhancing our view of how the trillions of microbes that co-exist in and around our bodies contribute to both health and disease. The research perfectly illustrates a "systems" approach that interactively integrates studies in mice as well as large-scale population science and smaller-scale human studies. It provides an entirely new and critical understanding of the dynamic interplay between the factors that predispose patients to CVD.

ENHANCING CLINICAL RESEARCH

As we work to integrate our research efforts across multiple disciplines, we are placing particular emphasis on ensuring that our clinical research is robust. A major challenge is to enhance clinical trials, which provide critical evaluation of new preventive and therapeutic approaches but are, arguably, some of our most challenging and expensive undertakings. In recent years, the NHLBI has been exploring ways

to make trials more efficient and more applicable to real-world clinical settings. Moving forward, we plan to build on past successes while capitalizing on new technologies and data sources, such as electronic medical records.

For many years, the NHLBI has used a network model to increase the efficiency of clinical trials. Our networks have a strong track record of conducting multiple, multi-center, clinical trials using standardized operations and sustainable infrastructures that minimize the time required to start new studies. They span a wide range of topics, such as asthma, cardiovascular cell therapy, pediatric heart disease, heart failure, childhood obesity, and transfusion medicine. A major problem facing our healthcare system is the costly cycle of chronic disease care that is characterized by persistent debilitating symptoms, hospitalizations for acute exacerbations of the condition, eventual hospital discharge, and then subsequent re-hospitalizations. To address this clinical practice challenge, the NHLBI is supporting innovation in discovery science that holds promise for breaking this vicious cycle of chronic heart, lung, and blood disorders. In 2014, we will pilot a new network structure to evaluate treatment strategies for acute, serious lung conditions—such as exacerbations of chronic obstructive pulmonary disease—that require hospitalization. If the new model proves successful we will apply it to clinical trials of other chronic diseases that are treated in inpatient clinical settings.

Another cost-effective strategy that the NHLBI has used very successfully is funding ancillary studies piggybacked onto trials to maximize return on investment. For example an NHLBI-funded clinical trial demonstrating that aspirin reduces the risk of heart attack also included ancillary studies that sought to identify new risk factors for CVD. These ancillary discovery science projects superimposed on the original clinical trial yielded strong evidence that elevated levels of a marker for inflammation called c-reactive protein are correlated with CVD events. The insights gained from the original clinical trial and subsequent ancillary studies have led to an innovative strategy to reduce CVD that targets the inflammatory process as a causative factor in heart attacks. Accordingly, the NHLBI recently funded the Cardiovascular Inflammation Reduction Trial to determine whether treatment with the anti-inflammation drug methotrexate, which is commonly prescribed for rheumatoid arthritis, reduces the risk of heart attacks and strokes. Taken together, these studies illustrate the NHLBI's ongoing efforts to enhance the efficiency and return-on-investment of our clinical trial portfolio so that advances in the practice of medicine are translated into healthier lives for all Americans.

We also are pursuing new opportunities to conduct trials that are bigger, but simpler, with clinically relevant end points that leverage routine medical care and existing data in electronic medical records and registries. By using electronic health records data from real-world clinical practice, we hope not only to make trials more relevant to clinical practice, but also to make the results more robust and reproducible by including hundreds of thousands of participants. In fiscal year 2014, the Institute will explore the use of electronic medical records in clinical trials through a new initiative to compare the ability of two data sources, electronic health records and traditional prospective patient-based clinical and research data, to answer research questions about pediatric pulmonary vascular diseases. We anticipate that these innovations that enhance the cost-effectiveness of NHLBI's approach to supporting clinical research will yield additional new discoveries that have a dramatic impact on the health outcomes of patients with chronic heart, lung, and blood disorders.

PREPARED STATEMENT OF RICHARD J. HODES, M.D.

Mr. Chairman and members of the committee: I am pleased to present the President's budget request for the National Institute on Aging (NIA) of the National Institutes of Health (NIH). The fiscal year 2014 budget includes $1,193,370,000, which is $72,979,000 more than the comparable fiscal year 2012 level of $1,120,391,000.

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 older age, profound changes will occur in our health care 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 gen-

eration of researchers who specialize in the issues of aging and old age. Finally, we support a vibrant program of basic, clinical, and translational research through our Intramural Research Program, which underwent a revision in 2013, to recognize new paradigms in the field of aging research and integrate laboratories and resources in a way that will more efficiently foster discovery.

IMPROVING THE HEALTH AND WELL-BEING OF OLDER AMERICANS

Life expectancy in the developed world has improved dramatically over the last century, and advances in public health and medicine are allowing people to stay healthier longer. But, since 1980, U.S. life expectancy, especially for women, has lagged behind other wealthy nations, and cross-national studies suggest that older Americans get sicker sooner than older Europeans. Similar disparities in health and longevity exist across geographical areas within the United States. NIA has established an initiative to identify and address the behaviors and social circumstances behind these differences.

NIA-supported investigators are continuing to work to identify the optimal means to address the unique health needs of older individuals. For example, studies have shown that regular physical activity can improve physical performance in older people, and with the U.S. Surgeon General, NIA has launched its nationwide "Go4Life" campaign to motivate older Americans to engage in physical activity and exercise. However, definitive evidence that physical activity can prevent mobility disability is lacking, and NIA supports the Lifestyle Interventions and Independence for Elders Study to assess whether a specific physical activity program can prevent disability in sedentary older individuals.

NIA-supported investigators are also testing interventions for health conditions common to old age. For example, the Centers for Disease Control and Prevention reports that fully half of older Americans have at least two chronic health conditions that compromise quality of life. NIA participates in a trans-NIH initiative to develop interventions to modify behavior and improve health outcomes among individuals with multiple chronic conditions. In addition, NIA supports research on rehabilitation from a number of acute and chronic conditions, including the development and pilot testing of a smart phone-based self-management system for older patients with heart failure and development of a unique biomaterial that can act as a temporary replacement for both bone and cartilage. Other ongoing studies include the ASPirin in Reducing Events in the Elderly (ASPREE) trial to determine whether the benefits of aspirin outweigh the risks in people over 70; testosterone supplementation to delay or prevent frailty in older men; exercise for mood, health, and cognition; and several interventions for menopausal symptoms.

THE FIGHT AGAINST ALZHEIMER'S DISEASE

It is estimated that as many as 5 million people in the United States aged 65 and older currently have Alzheimer's disease (AD), and annual costs of care for dementia, of which Alzheimer's is the most common cause, have been calculated using data from the Health and Retirement Study at between $157 billion and $215 billion among people 70 and older. Unless effective treatment or preventive interventions are identified, these numbers will rise significantly as the number of older Americans continues to increase. NIA has been a leader in the implementation of the National Alzheimer's Project Act and the development of the National Plan to Address Alzheimer's Disease. Recent initiatives have boosted support for AD research, including the NIH Director's allocation of an additional $50 million in fiscal year 2012 and $40 million in fiscal year 2013 for the disease. In the fiscal year 2014 President's budget request for NIA, $80 million of the increase planned for competing research project grants will be devoted to Alzheimer's disease projects, in response to recommendations of the Alzheimer's Disease Research Summit held in May 2012. The recent launch of the International Alzheimer's Disease Research Portfolio (IADRP), a publicly available database to capture the full spectrum of current AD research investments and resources throughout the world, will facilitate coordination of these efforts.

One active and highly promising area of research is the identification and elucidation of risk and protective genes for AD. For example, a variation in TREM2, a gene involved in inflammation and immune response, was recently identified as a moderate risk factor for late-onset AD, and a variant of the BCHE gene has been associated with deposition of beta-amyloid in the brain—a pathologic hallmark of the disease. Other investigators found that in mice, ApoE–4, the best-known genetic risk factor for late-onset AD, is associated inflammation of the blood vessels that feed the brain involving a molecule called cyclophilin A, suggesting that cyclophilin A may be a viable drug target. Finally, investigators with the NIH-supported AD

Genetics Consortium have identified a gene, ABCA7, which appears to be more strongly associated with AD in African Americans than in individuals of European ancestry. Further study is needed to confirm and extend this finding.

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. Funding for the groundbreaking Alzheimer's Disease Cooperative Study was renewed earlier this year, and several interventional studies are planned: a secondary prevention trial to test an amyloid-clearing drug in 1,000 symptom-free older volunteers with abnormal levels of brain amyloid accumulation; a randomized, controlled trial to find out if supervised aerobic exercise can influence cognitive decline, slow brain atrophy, or mitigate Alzheimer's pathology in older adults with mild cognitive impairment, a condition that often leads to AD; and a study to test the drug prazosin to help control agitation, a common symptom in AD patients.

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. The NIH Geroscience Interest Group (GSIG) was formed in 2012 to accelerate and coordinate efforts to promote discovery on the common risks and mechanisms behind age-related diseases and conditions. The GSIG has planned a number of initiatives for coming years, including informational activities, expansion of current initiatives to incorporate aging-related aims, and new trans-NIH funding initiatives. A GSIG workshop on inflammation and age-related diseases was held in September 2012, and a larger-scale workshop tentatively entitled "Geroscience: Foundations for Delaying Chronic Disease and Increasing Healthspan" is planned for fall 2013.

EMPOWERING THE NEXT GENERATION OF AGING RESEARCHERS

The need for health care professionals and research scientists who specialize in the unique needs of older individuals is becoming ever more urgent. Recently, NIA established the Grants for Early Medical/Surgical Subspecialists' Transition to Aging Research (GEMSSTAR) program to support 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.

PREPARED STATEMENT OF STORY C. LANDIS, PH.D.

Mr. Chairman and members of the committee: 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 2014 NINDS budget of $1,642,619,000 includes an increase of $19,275,000 over the comparable fiscal year 2012 level of $1,623,344,000.

COMBATING NEUROLOGICAL DISORDERS

The NINDS mission is to reduce the burden of neurological disorders through research. For stroke, research on prevention and treatment led to reductions of the age-adjusted death rate by 36.9 percent and of the actual number of deaths by 22.9 percent from 1999 to 2009.[1]

An intensive and inclusive NINDS planning process has identified the highest priority research investments to continue this progress against stroke. Experts across disciplines agreed that stroke clinical trials networks could accelerate progress. In response, NINDS is establishing a flexible stroke clinical trials network to conduct prevention, treatment, and recovery trials. With shared infrastructure, the network will better set priorities for studies, reduce cost and time in start-up, and therefore significantly improve efficiency. The network builds on lessons from the NeuroNEXT network, which expedites early phase clinical trials of new treatments, especially for rare diseases. NeuroNEXT uses a single Institutional Review Board and standard site contracts, which reduce time required to start a trial by months. It also accommodates projects from academic investigators or private partners. Trials for spinal muscular atrophy (SMA) biomarkers and secondary progressive multiple sclerosis

[1] "Circulation" 134:e6–245, 2013.

are under way, and planning has begun for clinical trials of two therapies developed by the NIH Therapeutics for Rare and Neglected Disease Program.

Reducing cognitive impairment from brain vascular disease is another priority that emerged from planning. Stroke itself is a major cause of dementia. Furthermore, the 7 million U.S. stroke survivors have an increased likelihood of cognitive problems, and the 13 million people with "silent strokes"[2] may also be at risk. Vascular risk factors are also associated with Alzheimer's disease. In fact, there is a spectrum from pure vascular dementia to pure Alzheimer's disease, with most patients having contributions from both.[3] This month a scientific workshop on Alzheimer's Related Dementias, part of the National Alzheimer's Project Act activities, focused on vascular dementia.

Traumatic Brain Injury (TBI) is the leading cause of death and disability in children and young adults, common among the elderly, and a major concern for the military and veterans. New studies will address two reasons why more than 30 major clinical trials of interventions for TBI failed to demonstrate improved outcomes: classification schemes do not distinguish between different types of damage in different parts of brain that may respond differently to interventions, and large variations in outcomes among medical centers confound assessment of interventions in clinical trials. A study of 1,000 children will evaluate the effectiveness of six major critical care guidelines for severe, pediatric TBI that lack compelling evidence. Another prospective, observational, multi-center study of 5,000 adults and children with TBI will be coordinated with studies by the European Union and the Canadian Institute of Health Research to enhance the statistical power to detect differences. The research community has agreed upon standards through the NINDS TBI Common Data Elements program that will allow meaningful comparison across studies, and the Department of Defense and NIH-led Federal Interagency TBI Research informatics system (FITBIR) provides a database for sharing information. NIH is also addressing TBI through the Foundation for NIH's Sports and Health Research Program, with support from the National Football League. In December a workshop focused on Chronic Traumatic Encephalopathy (CTE), a neurodegenerative disorder that can follow repetitive mild brain trauma in sports and the military. Follow-up research solicitations are underway, and this public private partnership will address other key aspects of sports and health in the coming years.

Epilepsy is another common disorder that affects people of all ages. Every 6 years since 2001, the Epilepsy Benchmarks process has brought NINDS, the research community, and non-governmental organizations together to establish research milestones and monitor progress. This April NINDS convened a major workshop to assess progress and set pathways forward. Previous Benchmarks guided investments that are now yielding important gene findings, advances in understanding how epilepsy develops, and attention to comorbidities, including Sudden Unexplained Death in Epilepsy (SUDEP). Future Benchmarks will focus on disease progression and modification, predictability of seizures and treatment response, and aspects of gender, ethnicity, and age (children and elderly), among other issues. Opportunities from other investments could also have a significant impact on epilepsy. The community is excited, for example, about advances in genetics, "big data," and brain circuit analysis.

Opportunities are also emerging for many other brain diseases, common and rare. Induced pluripotent stem cells derived from patients with Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's and other disorders allow laboratory testing of potential drugs. Biomarkers under development for Parkinson's, SMA, and other diseases will speed clinical testing. Brain stimulation therapies have proven benefit for Parkinson's disease, essential tremor, and dystonia, and show promise for diseases including epilepsy and Tourette syndrome. In research settings, brain machine interfaces enable paralyzed individuals to control a robotic arm and hand; development of practical devices is underway. Gene discoveries have led to mechanism targeted therapies that are now in the translational pipeline for many diseases, for example, muscular dystrophies, SMA, familial dysautonomia, and fragile X.

BASIC NEUROSCIENCE

Researchers in academia and industry agree that basic science drives progress against disease. A few recent examples: genes discovered for epilepsy, ALS, and autism enable the dissection of underlying disease mechanisms, pointing to potential targets for therapy development. Research is also revealing unexpected ways that

[2] "Circulation" 125:e2–e220, 2012.
[3] "Neurology" 72:368–74, 2009.

degeneration propagates in the brain, why acute pain can become chronic, and that serious disabilities in children born prematurely may be more reversible than expected. Science of the normal brain advanced this year on topics as diverse as the mechanisms of itch, how the brain clears waste, control of brain blood flow in infants, the influence of anesthetics on consciousness, and brain circuits for memory.

NINDS relies on investigator-initiated research throughout its programs. Engaging the insight and ingenuity of the scientific community in this way is especially crucial for basic research. The Institute has also emphasized the importance of transparent reporting of research findings, stressing rigor and reproducibility. A June 2012 NINDS workshop brought together representatives of all major stakeholders, which has already lead to changes within and outside the NIH, including policies of leading journals.[4]

Technology can also empower investigators. Investment by the NIH and others, together with advances in optics, computer science, genetic engineering, and other disciplines, has led to promising technological strategies to study the activity of large numbers of brain cells and the intricacies of their connections. The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative partners Federal agencies and private foundations in a coordinated program to develop and apply these emerging opportunities, including study of the human brain. This will ultimately revolutionize understanding of how networks of brain cells enable us to perceive, think, and act, and what goes wrong in diseases of the brain. A stellar committee of scientists will guide this initiative, with recommendations on first steps due this fall and a more complete plan the following summer. History suggests that the most important benefits of BRAIN will be those that we have not yet even imagined.

PREPARED STATEMENT OF HAROLD E. VARMUS, M.D.

Mr. Chairman and members of the committee: 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 2014 NCI budget of $5,125,951,000 includes an increase of $63,189,000 over the comparable fiscal year 2012 level of $5,062,762,000.

CANCER DEATHS CONTINUE TO DECLINE

The 2013 Report to the Nation on the Status of Cancer shows that overall cancer death rates continued to decline in the United States among both men and women, among all major racial and ethnic groups, and for all of the most common cancer sites, including lung, colon and rectum, female breast, and prostate. However, death rates continued to increase for melanoma of the skin (among men) and for cancers of the liver, pancreas, and uterus. The Report also emphasizes the importance of human papilloma virus (HPV) infection as a cause of the growing number of cancers, and shows that incidence rates are increasing for HPV-associated oropharyngeal and anal cancers. Also noted was that HPV vaccination coverage remains disappointingly low, falling short of the U.S. Government's Healthy People 2020 target, and much lower than vaccination rates reported in several other countries.

The continued decline in death rates for most cancers shows that our nation's investment in cancer research produces life-saving approaches to cancer control. However, there is still critical work to do, for example, in reducing tobacco exposure and obesity. Taken together, adverse health effects from cigarette smoking—including heart disease, stroke, and cancer—account for an estimated 443,000 deaths every year in the U.S.; nearly 1 in 5 deaths that could have been prevented. Since tobacco is responsible for about 30 percent of all cancer deaths in the U.S. (approximately 174,000 preventable cancer deaths in 2013), NCI continues to support research into methods to encourage smoking cessation and to discourage initiation; behavioral modification; and effectiveness of tobacco control efforts. Obesity, another significant cause of disease and preventable death, is associated with heart disease, stroke, type 2 diabetes and at least eight types of cancers. NCI funds research on the molecular mechanisms of obesity and cancer, and has developed new initiatives that explore ways to prevent and control obesity as a cancer risk factor.

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[4] e.g., "Nature" 490:187–91, 2012; "Nature" 496:398, 2013; "Nature Neuroscience" 16:1, 2013; 16:517, 2013.

NATIONAL CANCER INSTITUTE-SUPPORTED RESEARCH ADVANCES

The past year has yielded significant advances across the spectrum of cancer research, including studies of cancer mechanisms, prevention, detection, and therapy. One cancer detection study showed that the protein fibulin-3 may be able to identify patients with mesothelioma, suggesting that it may be a promising biomarker for high-risk populations exposed to asbestos. Another study found a way to target mesothelin, a cell surface protein that is present in normal tissues but overexpressed in more than 90 percent of pancreatic cancers and mesotheliomas, as well as in lung and ovarian cancers. Currently, the NCI intramural program is conducting a Phase I study of SS1P, an immunotoxin that targets mesothelin and destroys cancer cells, with plans for a Phase II study under way.

NCI is supporting research to identify the genetic drivers of cancer, and to advance adoption of precise tumor diagnosis and the development of targeted therapies. The two major genomics initiatives, involving hundreds of investigators nationwide, are The Cancer Genome Atlas (TCGA) and the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, focused on adult and pediatric cancers respectively. TCGA recently completed a study of lung squamous cell carcinoma that identified several potential therapeutic targets related to the initiation and progression of that disease. Another study examined nearly 400 endometrial (uterine) cancers and identified four new subtypes with several possible therapeutic targets. This study also found genomic similarities between endometrial and other cancers, including breast, ovarian, and colorectal. A TARGET study identified a subclass of acute lymphoblastic leukemia with high risk of recurrence associated with novel chromosomal translocations; these translocations represent exploitable therapeutic targets. Another TARGET study found few recurrent mutations among 240 cases of high-risk neuroblastoma, suggesting a limited number of targets for this pediatric disease.

In 2011, one of several noteworthy achievements was FDA approval of a new class of drug, vemurafenib, for the treatment of metastatic melanoma. The drug targets mutant forms of the BRAF protein, which is mutated in about 60 percent of these patients, leading to inhibition of a key growth pathway in the tumor cell, the MAPK pathway. Although the drug can increase the lifespan of these patients, almost all patients eventually develop drug resistance and relapse. Recent observations from several research groups have indicated that drug resistance can arise by any of several mechanisms. Some resistance is attributable to activation of the MAPK pathway, which can result from further mutation of BRAF itself or changes in other genes in the MAPK pathway. In other cases, resistance seems to result from activation of parallel pathways. These findings are now leading to clinical trials testing the hypothesis that combining the BRAF inhibitor with drugs that have been shown in preclinical models to reduce development of these resistance mechanisms will lead to longer therapeutic responses.

A potentially exciting therapeutic advance has come from immunotherapy research for B cell lymphoma being conducted at several institutions. The approach is to use genetic engineering to construct a chimeric antigen receptor (CAR) by combining parts from two different receptors, each with key immune functions, into one receptor that is then expressed by the patient's own normal T cells. Early-phase clinical trials with a receptor called anti-CD19 CAR, which works by directing T cells to the malignant B cells of the tumor, have resulted in several dramatic long-term responses in patients with advanced stage lymphoma.

PRECISION MEDICINE—APPROACHES TO CANCER

Incorporation of genomics into cancer research and clinical trials constitutes a growing portion of the Institute's research portfolio. In the years ahead, NCI and the entire cancer research enterprise will extend studies of the pathogenetic roles for specific genomic changes in tumors and test more interventions that are based on genetic profiles of tumors. There are several ways in which NCI is expanding its pursuit of these goals, most notably by mandating that all NCI-sponsored clinical trials include tissue collection and genomic analysis. NCI is also developing new approaches that explore the relationship between a cancer patient's genomic data (genotype) and the behavior of each patient's tumor (phenotype). One such study is the Exceptional Responders initiative, which will begin with phenotypes—asking why a small number of patients respond very well to a particular regimen, while the same treatment fails in almost all others with the same cancer type. To probe this phenomenon, researchers will explore the genomic data (genotype) to look for clues as to why some patients enrolled in clinical trials respond to agents that do not benefit most patients in the same study. Some recently reported cases provide dramatic evi-

dence for how a combination of molecular factors can explain why patients responded so well to therapy while comparable patients did not.

An approach from the opposite perspective (genotype to phenotype) is the "NCI MATCH" study, which aims to screen about 3,000 patients with advanced cancers in an effort to find approximately 1,000 such cancers with genetic mutations for which new therapies, including some not yet approved for use, are made available by the pharmaceutical industry through collaborative arrangements. This approach will provide a level of genomic data far beyond what would typically be available when genotyping is limited to one or more mutations known to be associated with a particular cancer type. There is a great opportunity for investigator-initiated research to build on information that emerges from this kind of novel trial, leading to yet greater therapeutic insight.

TARGETING RAS

The Frederick National Laboratory for Cancer Research (FNLCR) is a federally Funded Research and Development Center (FFRDC) supported by NCI, providing a national resource with unique capabilities for the development of new technologies and the translation of basic science discoveries into novel agents for the prevention, diagnosis and treatment of cancer and AIDS. NCI is poised to launch a large-scale project targeting RAS, an oncogene known for decades to drive the development of many types of cancers and about a quarter of all cancers in the U.S., including more than 90 percent of pancreatic adenocarcinomas. However, despite that information, the cancer research community has failed to develop effective treatments. Now, with the knowledge of new chemical approaches to inhibit the RAS protein directly and a deeper understanding of how RAS signaling works, NCI is launching a large-scale project to develop therapeutic strategies against cancers driven by RAS through a national "hub and spoke" model with scientific leaders, core facilities and important technologies at the FNLCR hub, and research led by investigators at companies, academic institutions and the NCI intramural research program at the spokes.

We find ourselves at a time of tremendous opportunity in cancer research, building our knowledge of the genetic changes that cause cancer, and finding new ways to use this information to diagnose, treat and even prevent cancers. The President's budget for 2014 for the National Cancer Institute will support studies intended to foster the discoveries essential for this next frontier of cancer research.

PREPARED STATEMENT OF THOMAS R. INSEL, M.D., DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

Mr. Chairman and members of the committee: I am pleased to present the President's budget request for the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH). The fiscal year 2014 NIMH budget of $1,465,782,000 represents a decrease of $11,734,000 below the comparable fiscal year 2012 level of $1,477,516,000. In my statement, I will review the scope of mental disorders in the United States and their impact on public health, and I will outline examples of NIMH's research efforts designed to address this challenge.

PUBLIC HEALTH BURDEN OF MENTAL ILLNESS

The National Institute of Mental Health (NIMH) is the lead Federal agency for research on mental and behavioral disorders, with a mission to transform the understanding and treatment of mental illnesses through basic and clinical research. The global burden of mental illness is enormous. An estimated 11 million American adults (approximately 5 percent of all adults) suffer from a seriously disabling mental illness each year.[1] Mental disorders are the leading cause of disability in the United States and Canada, accounting for 28 percent of all years of life lost to disability and premature mortality (Disability Adjusted Life Years or DALYs) for people age 15–49.[2] The personal, social, and economic costs associated with these disorders are tremendous. A cautious estimate places the direct and indirect financial costs associated with mental illness in the U.S. at well over $300 billion annually, and it ranks as the third most costly medical condition in terms of overall

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[1] Substance Abuse and Mental Health Services Administration. "Results from the 2009 National Survey on Drug Use and Health: Mental Health Findings" (Office of Applied Studies, NSDUH Series H–39, HHS Publication No. SMA 10–4609). Rockville, MD: Substance Abuse and Mental Health Services Administration, 2010.

[2] The World Health Organization. "The global burden of disease: 2004 update," Table A2: Burden of disease in DALYs by cause, sex and income group in WHO regions, estimates for 2004. Geneva, Switzerland: WHO, 2008.

healthcare expenditure, behind only heart conditions and traumatic injury.[3] [4] Even more concerning, the burden of illness for mental disorders is projected to sharply increase over the next 20 years.[5]

NIMH-supported research has found that Americans with serious mental illness (SMI)—in which the ability to function in daily life is significantly impaired—die 8 years earlier than the general population.[6] People with SMI experience chronic medical conditions and the risk factors that contribute to them more frequently and at earlier ages. There are low rates of prevention, detection, and intervention for chronic medical conditions and their risk factors among people with SMI, and this contributes to significant illness and earlier death.

PREDICTING AND PREVENTING PSYCHOSIS

In the past, we viewed mental disorders as chronic conditions defined by their apparent symptoms, even though behavioral manifestations of illness are in fact the last indications—following a cascade of subtle brain changes—that something is wrong. We understand now that mental disorders are brain disorders, with specific symptoms rooted in abnormal patterns of brain activity. Moving forward, NIMH aims to support research on earlier diagnosis and quicker delivery of appropriate treatment, be it behavioral or pharmacological.

The majority of people with serious mental illness (SMI)—in which the ability to function in daily life is significantly impaired—experience significant delays to seeking care—nearly 2 years, on average.[7] [8] Untreated SMI, particularly psychosis, poses an increased risk for using potentially life-threatening, self-administered treatments, such as legal or illicit substances, potentially resulting in death. When untreated psychosis is also accompanied by symptoms of paranoia and when it is associated with substance abuse, the risk of violence is increased. Importantly, the risk of violence is reduced with appropriate treatment.[9] [10] Moreover, people with SMI are 11 times more likely than the general population to be victims of violence.[11] Therefore, NIMH has planned several new research initiatives, ramping up the Institute's commitment to early treatment in order to reduce this period of untreated psychosis to less than 12 weeks. These initiatives propose two objectives: (a) improving detection of youth and young adults at high risk for psychosis; and (b) reducing the duration of untreated psychosis in community treatment settings.

IMPROVING PUBLIC HEALTH

When violence is associated with mental illness, it is most often self-directed. Approximately 5 percent of individuals with schizophrenia will die by suicide during their lifetime, a rate 50-fold greater than the general population.[12] Furthermore, suicide is the 10th leading cause of death in the United States, accounting for the loss of more than 38,000 American lives each year, more than double the number

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[3] Insel TR. Assessing the economic cost of serious mental illness. "Am J Psychiatry." 2008 Jun;165(6):663–5.

[4] Soni A. "The Five Most Costly Conditions, 1996 and 2006: Estimates for the U.S. Civilian Noninstitutionalized Population." Statistical Brief #248. July 2009. Agency for Healthcare Research and Quality, Rockville, MD.

[5] Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, Feigl AB, Gaziano T, Mowafi M, Pandya A, Prettner K, Rosenberg L, Seligman B, Stein A, Weinstein C. "The Global Economic Burden of Non-communicable Diseases." Geneva, Switzerland: World Economic Forum, 2011.

[6] Druss BG, Zhao L, Von Esenwein S, Morrato EH, Marcus SC. Understanding excess mortality in persons with mental illness: 17-year follow up of a nationally representative U.S. survey. "Med Care." 2011 Jun;49(6):599–604.

[7] Wang PS, Berglund PA, Olfson M, Kessler RC. Delays in initial treatment contact after first onset of a mental disorder. "Health Serv Res." 2004 Apr;39(2):393–415.

[8] Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients. "Arch Gen Psychiatry." 2005 Sep 62:975–983.

[9] Swanson JW, Swartz MS, Van Dorn RA, Volavka J, Monahan J, Stroup TS, McEvoy JP, Wagner HR, Elbogen EB, Lieberman JA; CATIE investigators. Comparison of antipsychotic medication effects on reducing violence in people with schizophrenia. "Br J Psychiatry." 2008 Jul;193(1):37–43.

[10] Steadman HJ, Mulvey EP, Monahan J, Robbins PC, Appelbaum PS, Grisso T, Roth LH, Silver E. Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods. "Arch Gen Psychiatry." 1998 May;55(5):393–401.

[11] Teplin, LA, McClelland, GM, Abram, KM & Weiner, DA. Crime victimization in adults with severe mental illness: comparison with the National Crime Victimization Survey. "Arch Gen Psychiatry," 2005, 62(8), 911–921.

[12] Hor K. & Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. "J Psychopharmacol." 2010;24(4S): 81–90.

of lives lost to homicide.[13] NIMH is spearheading several initiatives intended to reduce and prevent suicide, such as taking a lead role with The National Action Alliance for Suicide Prevention, a public-private partnership tasked with developing the next National Strategy for Suicide Prevention. Alongside the Jed Foundation, NIMH is co-chairing the Action Alliance's Research Task Force (RTF), which is developing a National Research Agenda to reduce suicide morbidity (attempts) and mortality (deaths) by at least 20 percent in 5 years, and 40 percent or more in 10 years. The RTF aims to release the Agenda in September 2013.

One of the most notable and disturbing increases in suicide over the past decade has occurred among the Nation's returning military veterans. To counter this trend, NIMH has partnered with the Department of the Army to conduct the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) Project—the largest study of mental health risk and resilience ever conducted among military personnel. Army STARRS seeks to identify factors that both protect soldiers' mental health and those that put a soldier's mental health at risk. The goal is to provide empirical evidence to help the Army develop targeted prevention and treatment strategies. Army STARRS has established a data enclave that integrates the administrative records of the 1.6 million soldiers who served between 2004 and 2009. In addition, Army STARRS includes a series of studies involving soldiers currently serving on active duty. Most of these studies have now finished enrolling subjects and the data are being analyzed.

NIMH, along with other NIH Institutes and the Departments of Defense, Education, and Veterans Affairs are contributing to the development of the National Research Action Plan (NRAP), pursuant to Executive Order, "Improving Access to Mental Health Services for Veterans, Service Members, and Military Families" (http://www.whitehouse.gov/the-press-office/2012/08/31/executive-order-improving-access-mental-health-services-veterans-service). NRAP will strategically inform planning for future federally funded research related to mental health and traumatic brain injury among veterans and soldiers. NRAP will address post-traumatic stress disorder, depression, suicide prevention, and some aspects of substance abuse prevention and treatment.

THE FUTURE OF MENTAL HEALTH RESEARCH

On April 2, President Obama proposed the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative (http://www.nih.gov/science/brain/index.htm), a bold plan not only to transform our fundamental understanding of the brain, but also to revolutionize both our approach to brain research and our understanding of brain disorders. BRAIN will encourage the development of innovative technology necessary for monitoring the activity of millions of brain cells simultaneously and translate that activity into circuit diagrams and algorithms. This effort will advance our understanding of how the brain works and fails to work, and how it can be repaired.

Research has taught us to detect diseases early and intervene quickly to preempt later stages of illness. This year, we will avert 1.1 million deaths from heart disease because we have not waited for a heart attack to diagnose and treat coronary artery disease.[14] Our best hope of reducing mortality from mental illness and other brain disorders will come from realizing that just like other medical disorders, we need to diagnose and intervene before the symptoms become manifest. Our investments today ensure a healthy tomorrow.

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

Mr. Chairman and members of the committee: 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 2014 NIDCR budget of $411,515,000 includes an increase of $1,568,000 over the comparable fiscal year 2012 level of $409,947,000.

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[13] Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS): www.cdc.gov/ncipc/wisqars accessed May 2013.

[14] Vital Statistics of the United States, CDC/National Center for Health Statistics. (2011, August). Age-adjusted Death Rates for Coronary Heart Disease (CHD). National Heart Lung and Blood Institute. Retrieved January 23, 2013, from http://www.nhlbi.nih.gov/news/spotlight/success/conquering-cardiovascular-disease.html.

When NIDCR was established as a research home for oral health in the mid-20th century, it focused primarily on oral infectious diseases like tooth decay and periodontal disease. Today, the Institute maintains a diverse and productive research portfolio that extends beyond infections in the mouth. In keeping with its mission to improve the Nation's oral health, the breadth of NIDCR-funded research includes basic science studies aiming to understand development, maintenance, and regeneration of tissues of the face and head; novel preventive, diagnostic, and treatment approaches for oral infections and oral cancer; investigating the role the mouth plays as an indicator of overall health; and community-led studies of issues related to dental care.

REALIZING PERSONALIZED ORAL HEALTH

Personalized health, aiming to individualize care based on a person's unique genetic, environmental, and clinical profile, is not new: dentists and physicians have long recognized variations among patients, and they have provided customized care based on the history, environmental exposure, and behavioral components that shape a person's health. However, new technologies offer additional strategies. For example, the NIDCR investment in molecular diagnostics using saliva is a key step toward advancing personalized care. As a diagnostic fluid, saliva has long been recognized to have many advantages over blood. These include simple, non-invasive collection; the potential for lower testing costs; portability; and application at or near the site of patient care, maximizing convenience and allowing the results to be available immediately to the patient. Recent progress comes from NIDCR-supported scientists that developed a miniaturized, portable biochip that can analyze small volumes of saliva. During the first phase of this project, the researchers found promising predictive markers for cardiac events. Other research identified the presence, in saliva, of disease-related proteins and RNAs for oral cancers, Sjögren's syndrome, and conditions such as periodontal disease.

Beyond supporting the development of molecular-based tools to individualize care, NIDCR appreciates the important role of behavior and environment in determining an individual's health status. As trusted providers in a private setting, dentists have an extraordinary opportunity to communicate to their patients the health risks of behaviors such as alcohol and tobacco use. NIDCR-funded projects are currently exploring how dental providers can help their patients by providing smoking-cessation advice.

PROGRESS IN ORAL DISEASES: CANCER

The 5-year relative survival rate for oral and pharyngeal cancer is approximately 60 percent, which is among the lowest for all major cancers.[1] This outlook is significantly worse for African Americans, who face a 5-year relative survival rate close to 40 percent. In addition to bringing behavioral science tools and expertise to bear on this problem, NIDCR aims to initiate and lead an NIH-wide effort in oral premalignancy identification and oral cancer prevention. The multi-pronged approach weaves together scientific advances in molecular profiling with clinical testing of the FDA-approved drug rapamycin for its effectiveness against certain cancers of the head and neck. Also, in fiscal year 2014 NIDCR will launch an initiative supporting research on a unique type of cell capable of initiating oral cancer, as therapies targeting these cells could potentially eliminate the "root" of the cancer.

Infection with human papillomavirus (HPV) is an increasingly recognized risk factor for distinct forms of oral and pharyngeal cancer. NIDCR remains vigilant to this rising public health concern. The incidence of HPV-linked oral cancers in the United States has been increasing at a rapid rate—by 225 percent from 1998 to 2004, and now 37 percent of oral and pharyngeal cancers are HPV-associated cancers.[2] Because the FDA-approved HPV vaccine Gardasil is effective against the particular strains of HPV implicated in oral cancers, NIDCR is supporting efforts to determine the potential benefit of this vaccine in preventing these terrible diseases.

PROGRESS IN ORAL DISEASES: PAIN

NIDCR has a long-standing interest in the understanding and management of chronic pain. In 2012, the Institute launched the second phase of Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), the first-ever large, prospective clinical study to identify risk factors for temporomandibular joint disorder (TMJD). OPPERA II will follow more than 3,000 initially pain-free individuals for

[1] Siegel et al., (2013) Cancer statistics, 2013. "CA: A Cancer Journal for Clinicians." 63 (1) 11–30.

[2] Gillison ML et al. (2012) "JAMA";307,693–703; Jemal A et al. (2013) "J Natl Cancer Inst."

three to 5 years. OPPERA II will build upon OPPERA I and further explore risk factors and genome-wide markers for chronic TMJD as well as for several frequently overlapping pain conditions. Also in 2012, NIDCR partnered with the National Institute of Neurological Disorders and Stroke to host a workshop focused on identifying innovative scientific approaches to the study of chronic overlapping pain conditions. Together, these efforts are expected to have an impact not only on TMJD, but also on other chronic pain conditions including fibromyalgia, irritable bowel syndrome, chronic headache, vulvodynia, and chronic fatigue syndrome. In addition, NIDCR co-sponsored a meeting in 2013 with two other NIH Institutes to explore opportunities to utilize contemporary and integrative approaches in understanding TMJ structure and function, including novel imaging and molecular diagnostic techniques.

SYSTEMS APPROACHES TO UNDERSTANDING ORAL HEALTH

Oral tissues and fluids have remarkable protective roles, dependent on human components and those of oral bacteria. The NIH Human Microbiome Project (HMP) has created unprecedented opportunity to learn much more. NIDCR is harnessing HMP knowledge and tools to define the overlapping and unique roles of the oral microbiota in oral diseases and immune function—such as in susceptibility to autoimmune diseases and cancer—and in other systemic conditions like metabolic syndrome, a cluster of co-occurring conditions including increased blood pressure, blood sugar levels, body fat, and cholesterol levels that can raise the risk of heart disease, stroke, and diabetes. NIDCR is investing resources in new approaches to understand the properties of the vast majority (more than 80 percent) of the microbial universe in our mouths that cannot be grown in the laboratory. These studies will provide insights into interactions among microbes and with human cells, potentially leading to the development of novel strategies for prevention, diagnosis, and treatment of oral diseases.

Genome-wide association studies, or GWAS, are another example of the broad utility of systems approaches for investigating oral health biology. GWAS methods combine human genome sequencing and high-speed computing, to scan the entire genome for disease triggers and factors. In the realm of oral health, GWAS suggest that the risk for dental caries arises from interplay between genetic factors, home fluoride exposure levels, and in some cases, taste preferences. Further analyses may point to common risk factors for dental caries and other conditions such as diabetes and cardiovascular disease. NIDCR-funded genetic studies of craniofacial development and birth defects have yielded information on the causes of cleft lip and palate and craniosynostosis, and this research will continue to be a focus moving forward.

NEW DIRECTIONS IN ORAL HEALTH RESEARCH

Minding workforce trends and the importance of interdisciplinary science to health promotion, NIDCR recognizes the need for investigators representing a range of scientific areas to conduct research in dental, oral, and craniofacial health. NIDCR is particularly engaged with the needs and contributions of practitioners, whose participation in research could cut the time it takes for laboratory research to be applied for patients. In 2005, NIDCR launched the Practice-Based Research Network, or PBRN, and the second, 7-year phase began in April 2012. This powerful "real world" research network is recruiting practitioners in every State—with a goal of involving at least 5,000—to propose and perform clinical studies on topics important to dentistry. Because the research is conducted by clinicians in their own practices, 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 yield more individualized and evidence-based treatment and prevention, to the benefit of millions of Americans.

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 committee: I am pleased to present the President's fiscal year 2014 Budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The fiscal year 2014 budget includes $1,811,786,000, which is $18,080,000 above the comparable fiscal year 2012 appropriation of $1,793,706,000. Complementing these funds is an additional $150,000,000 also available in fiscal year 2014 from the Special Statutory Funding Program for Type 1 Diabetes Research. 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.

TODAY'S BASIC SCIENCE FOR TOMORROW'S BREAKTHROUGHS

NIDDK-supported basic science research is achieving remarkable advances and building the foundation for previously unimaginable strategies to improve health and quality of life. Among these advances, recent research into biological processes showed that two newly discovered molecules—irisin and TRPV4—regulate energy expenditure in mice. Irisin was shown to promote energy expenditure (calorie burning), and reduced obesity and type 2 diabetes. Mice genetically engineered to lack TRPV4 had increased energy expenditure without differences in food intake, physical activity, or body temperature. If these findings are extended to humans, administration of irisin or targeting of TRPV4 could be potential new therapeutic approaches for obesity and type 2 diabetes. In addition, newly identified brown fat progenitor cells and factors that regulate brown fat development may lead to new obesity therapies that coax cells in white fat tissue to burn calories faster, like brown fat. The microorganisms that inhabit the gastrointestinal tract are important factors in maintaining or tipping the balance between digestive health and disease. Investigators have also reported that early exposure to "friendly" microbes protects against inflammatory bowel disease in animal models. Investigating the different types of bacteria that reside in the intestines, researchers have discovered surprising links to diet, diversity with respect to age and geographic location, fatty liver disease, and antibiotic exposure. Scientists supported by our Institute have shown that pancreatic β cells can revert to an earlier developmental stage and lose their ability to produce insulin; thus, approaches that save cells that have regressed and restore them to become β cells again could be an effective way to treat type 2 diabetes. Other scientists have illuminated the complex system of regulation surrounding kidney fibrosis following injury, and identified potential targets for further strategies aimed at preventing and possibly reversing kidney fibrosis. For example, one molecule, called microRNA–21, was found to be highly elevated in two mouse models of kidney disease soon after injury but before fibrosis appeared. Mice engineered to lack the microRNA–21 gene showed diminished fibrosis in response to kidney injury. This molecule, which is found in humans with kidney injury, represents a potential target for antifibrotic therapies in kidney disease.

NIDDK 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. Areas of emerging opportunity include research on human β cells toward the goal of developing cell replacement therapies; genetic analyses to identify genes and gene regions associated with inflammatory bowel disease; identification of environmental triggers of type 1 diabetes in genetically susceptible newborns; and development of blood and urine tests to better predict patients who will have rapid progression of kidney disease or worsening of heart disease.

TRANSLATIONAL AND CLINICAL SCIENCE

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 have recently reported that weight loss and increased physical fitness slow decline in mobility in overweight or obese adults with type 2 diabetes. Invasive and costly tests commonly performed in women before surgery for stress urinary incontinence may not be necessary—information that women and their physicians can consider in planning treatment. This could result in fewer unnecessary procedures and a savings in healthcare costs. Additional research has shown that interventions to prevent type 2 diabetes in people at high risk for the disease are a very cost-effective way to improve their health and quality-of-life.

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 are conducting two large-scale, long-term observational studies of chronic kidney disease (CKD), the Chronic Kidney Disease in Children (CKiD) Study and the Chronic Renal Insufficiency Cohort (CRIC) Study, to address a wide range of scientific questions focused on prediction and mechanisms of CKD progression in both children and adults. Several efforts are translating CKD research into improved clinical outcomes such as decision support interventions to improve renal replacement therapy preparation. Among multifaceted efforts to meet the challenge of obesity is a consor-

tium studying lifestyle interventions for overweight and obese pregnant women, to improve the health of both mother and child. The Institute continues to support clinical studies for a range of liver diseases including a multicenter research network planning trials of different treatment strategies for hepatitis B, including comparative effectiveness research. The MERIT-UC study investigators are conducting a multicenter trial to investigate the safety and efficacy of methotrexate (a drug also used to treat some forms of cancer and rheumatoid arthritis) in adult patients with active ulcerative colitis. The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness study has as its overarching goal to understand the relative effectiveness of different medications in combination with metformin, and whether introducing them sequentially or initially in combination is most effective in maintaining glycemic goals over time in patients with type 2 diabetes. To maximize the reach and benefits of interventions proven successful in clinical trials, NIDDK will sustain support for translational research.

RECRUITING AND RETAINING DIVERSE SCIENTIFIC TALENT

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. This year, NIDDK held its 11th annual Network of Minority Research Investigators workshop to encourage and facilitate participation of underrepresented racial and ethnic minority groups in the conduct of biomedical research. Several NIDDK-sponsored programs provide opportunities for minority students to obtain research experience. For example, NIDDK's Short-Term Education Program for Underrepresented Persons, or STEP-UP, provides research education grants to seven institutions to coordinate three high school and four undergraduate STEP-UP programs that enable students to gain summer research experience and training. STEP-UP and the NIH Building Infrastructure Leading To Diversity (BUILD) Consortium will work to identify resources which may be shared and to exchange lessons learned/best practices.

INTEGRATING SCIENCE-BASED INFORMATION INTO PRACTICE: EDUCATION AND OUTREACH

NIDDK also will continue to support education, outreach, and awareness programs. In 2012, NIDDK, in collaboration with NLM, launched the LiverTox database—a free source of evidence-based information for healthcare professionals and for researchers studying liver injury associated with prescription and over-the-counter medications, herbal products, and dietary supplements. Likewise, in 2012, NIDDK collaborated with Home Box Office to develop "The Weight of the Nation" documentary series showing how obesity affects the Nation's health, and how interventions can turn the tide against obesity and its complications. In addition, NIDDK's National Kidney Disease Education Program collaborated with the American Diabetes Association's "Live Empowered" program, the National Coalition of Pastors' Spouses, and Chi Eta Phi Sorority, Incorporated, to kick off the first nationwide "Kidney Sundays" event to raise awareness of kidney disease risk factors among African Americans.

In closing, NIDDK's future research investments 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.

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

Mr. Chairman and members of the committee: 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 2014 budget of $2,401,011,000 includes a decrease of $24,511,000 below the comparable fiscal year 2012 level of $2,425,522,000.

Basic discovery for better health is the past, present, and future of NIGMS. Today, amid the breakneck speed of progress in biomedical and information science technology, truly phenomenal opportunities for progress are at our doorstep.

In one recent example of the merit of joining the biological and information sciences, scientists with the NIGMS-led NIH Pharmacogenomics Research Network (PGRN) devised a computer algorithm to sift through millions of reports to the U.S. Food and Drug Administration to predict dangerous, yet unsuspected interactions

between medications such as those between antidepressants and a common blood-pressure medication. In another case, researchers with the Institute's flagship Protein Structure Initiative (PSI) solved the three-dimensional atomic structure of the molecule on the surface of brain cells that attaches to opioids and is centrally involved in pleasure, pain, addiction, depression, psychosis, and related conditions. By linking these conditions in molecular terms, the research may well lead to better, more targeted drug therapies for a range of brain-related conditions. A third example comes from investigators with the NIGMS-funded Models of Infectious Disease Agent Study (MIDAS) program. They showed that methicillin-resistant "Staphylococcus aureus", or MRSA, infections are better prevented when hospitals cooperate and coordinate their infection control procedures. This research points to policy-related measures that could have a significant impact on public health.

FROM BENCH TO BEDSIDE AND BACK

For several decades, NIGMS has provided a home for research conducted in emergency care settings. The Institute's burn and trauma centers have made many discoveries that have been implemented clinically. These include the development of artificial skin for burn victims, nutritional standards for the care of severely injured patients, and new understanding of how inflammation affects injury and healing in people who have experienced severe physical trauma.

This past year, NIGMS announced the formation of the Office of Emergency Care Medicine (OECR). This office is the culmination of several years of discussions between NIH and the emergency medicine community, and responds to reports about the Nation's emergency medical system issued in 2006 by the Institute of Medicine. Although OECR does not have funding authority, it will provide agency-wide coordination toward speeding diagnosis and improving care for the full spectrum of conditions that require emergency treatment.

Another compelling example of the clinical relevance of NIGMS-supported basic research is the Developmental Genome Anatomy Project (DGAP), which employs a model of "patient as laboratory." DGAP scientists identify abnormalities in the DNA of people with a disorder that is not well understood, and then follow up with laboratory studies to further probe the molecular defect in animal models. One exciting DGAP discovery is a prenatal diagnostics method that analyzes DNA in amniotic fluid using customized whole-genome sequencing.

BASIC DISCOVERIES FOR BETTER HEALTH

NIGMS-supported research employs a range of non-human model organisms to ask and answer questions about human biology. One example is research to understand circadian rhythms, commonly known as the biological clock. The foundation of knowledge gathered over the years in this area of science is now coming together to help explain how various diseases and conditions are influenced by the time of day. Recent NIGMS-funded studies have shown that circadian rhythms have a major influence on the production of the basic units of metabolism such as amino acids, sugars, and fats. Researchers learned that about 60 percent of these essential metabolites that sustain and promote cell health and growth are synchronized with the body's clock system. These findings are important because of their connection to other NIGMS-supported research established a link between circadian rhythms and chronic conditions like diabetes and obesity, which involve activities linked to time of day including eating, sleeping, and physical activity. Integrating knowledge from basic metabolism and circadian biology has implications for managing the many conditions related to our biological clocks.

Aside from their use as models for basic cell biology, genetics, and metabolism, bacteria are a focus of study for NIGMS-supported researchers in another way: the study of bacterial communities called biofilms. Many individual microbes do not cause disease; indeed, they aid in normal digestion and perform other vital roles in the body. Yet, when some otherwise non-harmful strains of bacteria assemble into a film structure, they can clog medical devices like heart valves and catheters. Using powerful microscopes and time-lapse imaging, NIGMS-supported scientists watched biofilms form, as microbes joined together to create slimy ribbons that ensnared other bacteria as they traveled through narrow, fluid-filled tubes mimicking implanted medical devices. The researchers were surprised to learn just how fast this clogging occurred, and with no apparent warning. These research results could be used toward the development of clog-resistant medical devices.

ENABLING TECHNOLOGY THAT ADVANCES DISCOVERY

Technology is a key driver of progress in biomedicine. NIGMS considers its support of resource development a vital component of the Institute's investment in al-

lowing creative scientists to uncover new knowledge and make breakthrough discoveries.

One example of NIGMS-supported resource development is the NIGMS Biomedical Technology Research Centers program, a synergistic interaction of technical and biomedical expertise. These Centers promote the widespread and routine application of pioneering technologies and methods, and apply them to a broad range of basic, translational, and clinical research efforts. The resources—ranging from electron microscopes to bioinformatics platforms to mass spectrometers and other technologies—are used by thousands of NIH-supported scientists each year.

A second example is the Institute's investment in research on chemistry methods that can be used and re-purposed by both academia and industry. In one recent instance, scientists used NIGMS research funds to make a chemistry toolkit that can quickly and easily generate dozens or even hundreds of versions of a single molecule, toward the testing and refining of such molecules as potential drugs. This research is important because companies are unlikely to sponsor the development of broad-based resources like this. A key advantage of this new technique is that it simplifies complicated and potentially hazardous chemical reactions such that they can be automated and can be performed in a water-based environment without the use of harmful chemicals.

STRATEGY FOR THE FUTURE

NIGMS has always planned strategically for the future, since biomedical research is a long-term commitment to supporting creative people to develop and test new ideas. Part of this process is keeping an eye on the evolution of biomedicine as new tools emerge and new disease threats come to light. In recent years, NIGMS has published companion strategic plans that chart the Institute's course for research and research training, noting the tight link between the two. The Institute continues to invest funds and resources toward activities that reflect the content of these plans. NIGMS strives for a healthy balance within its scientific portfolio between small projects that are conducted by individual scientists within their laboratories, and larger consortia (like the PGRN, PSI, and MIDAS) that enable researchers to work together on problems that call for a broader range of expertise, samples, and resources than can be managed reasonably and successfully by individual scientists.

NIGMS is pleased that many of its research and research training efforts under way resonate so well with recommendations put forth last year by the NIH Advisory Committee to the Director on NIH's role in research training and in promoting a diverse biomedical workforce. Toward building a strong evidence base in workforce-related issues, NIGMS has funded grants that investigate factors contributing to gender and ethnic/racial disparity in workforce representation, to increase diversity. Emerging concepts include eliminating unconscious bias, career flexibility, and the value of good mentoring. This growing body of work will be pivotal to effecting change on a larger scale.

NIGMS recognizes its vital role in supporting basic research for better health. In so doing, the Institute contributes in a sustained fashion to the health of the American people and to maintaining America's leadership role in science.

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 committee: I am pleased to present the President's budget request for the "Eunice Kennedy Shriver" National Institute of Child Health and Human Development (NICHD). The fiscal year 2014 budget of $1,339,360,000 includes an increase of $20,417,000 over the comparable fiscal year 2012 level of $1,318,943,000.

This past year, NICHD celebrated its 50th anniversary. Beyond celebrating past accomplishments, this milestone inspired the Institute, along with its many stakeholders, to identify compelling scientific opportunities for the next decade. The Institute's future research must build upon its strong foundation of scientific advances, from better understanding of the basic mechanisms that transform cells into healthy and effectively functioning individuals, to clinical studies that improve the health and well-being of women, children, families, and individuals with disabilities.

DEVELOPMENTAL BIOLOGY

Research in developmental biology helps to explain how individuals develop and the origins of various diseases and conditions. Recently, NICHD-funded scientists found that pregnant women with epilepsy who took the prescription drug topiramate during their first trimester to prevent seizures were at a slightly increased risk of having babies with cleft lip. Intramural scientists recently used next-generation gene sequencing techniques to discover new brain regions in an animal model, once thought to be inert, which appear to be active in the pineal gland, which controls the body's 24-hour wake-sleep cycle and is integral to development. Advances in genetics and systems biology will shed new light on human development, and provide critical underpinnings for emerging fields such as regenerative medicine.

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Complex interactions among biological and external factors, starting before conception, can influence health across the life course, and even across generations. NICHD researchers discovered a genetic pathway common to the rapid growth of healthy fetuses and the uncontrolled cell division of cancer, shedding light on both normal development and the genetic bases of common cancers. Understanding the developmental origins of health and disease will benefit from interdisciplinary and global studies and, ultimately, can be applied to prevent, treat, or even reverse chronic conditions such as obesity, diabetes, and cognitive deterioration.

PREGNANCY AND PREGNANCY OUTCOMES

Achieving a better understanding of pregnancy processes and fetal development can pave the way for predicting and preventing poor pregnancy outcomes as well as improving lifelong health for both women and infants. A new NICHD-funded study reported that pregnant women's exposure to the flu was associated with a nearly four-fold increased risk that their children would develop bipolar disorder in adulthood. This information may encourage and increase the use of prevention strategies, such as the flu vaccine. Another study found that women who develop gestational diabetes during pregnancy can greatly decrease their risk of developing type 2 diabetes later in life by maintaining a healthy diet in the years following pregnancy. Targeted areas for future research include obtaining further understanding of how to promote healthy pregnancies and unraveling the complex causes of stillbirth and prematurity.

REPRODUCTION

Reproductive health is an essential element of personal well-being across the lifespan, and necessary to ensuring the health of future generations. NICHD-supported research found that the hormone progestin, often given as a first step in infertility treatment for polycystic ovary syndrome, unexpectedly decreased the odds of conception and giving birth. Discoveries such as this advance our understanding of what works in clinical practice and what may have unintended consequences and, at the same time, be used to identify potential new diagnostic and therapeutic targets for managing critical aspects of women's and men's reproductive health.

BEHAVIOR AND COGNITION

Human behaviors can contribute to positive health outcomes or increase the risk of adverse ones. NICHD-funded researchers found that when the mind is at rest, the electrical signals by which brain cells communicate appear to travel in reverse, wiping out unimportant information, while sensitizing cells for future learning. NICHD research found that children who failed to acquire a particular math skill, number system knowledge, in first grade scored well behind their peers by seventh grade, pointing the way for targeted intervention when it matters most. In another study, seven-month old babies who were later diagnosed with autism took slightly longer to shift their gaze than babies who developed normally, which may provide an early clue to differences in their brain structure. Future basic and translational research that combines neuropsychological, behavioral, and social science perspectives will increase knowledge about the mechanisms that underlie typical and atypical behavior and cognition.

PLASTICITY AND REHABILITATION

Plasticity, adaptive or maladaptive change at the cellular, tissue, organ, or system levels, is at the core of human development and rehabilitation. NICHD researchers

have identified proteins in an animal model that help fuse early-stage cells and eventually develop into muscle cells. This finding has implications for understanding how to repair and rehabilitate muscle tissue and how specialized cells (osteoclasts) repair and maintain bones. The ongoing challenge for scientists will be to generate additional knowledge about the mechanisms of plasticity, and translate this knowledge into interventions that can help individuals remodel, maintain, or enhance functioning.

POPULATION DYNAMICS

Individuals, families, and communities are all critical units, through which population-level factors interact with genetic and environmental variables, influencing individual health across the lifespan. An NICHD study demonstrated that the stresses of poverty (e.g., financial worries, inadequate child care), were shown to lead to impaired learning ability in children; high levels of stress hormones influence the developing circuitry of children's brains, impairing their executive functions. Another study, a landmark collaboration among NICHD, other NIH Institutes and Centers, Federal agencies, and private foundations, demonstrated that providing specialized housing vouchers that enabled low-income women and children to move from impoverished neighborhoods to those with relatively few poor residents reduced extreme obesity and diabetes over time. Over the next decade, research must continue to provide the comprehensive evidence needed for what works and how to scale programs at the population level, accounting for individual behaviors and biomedical factors, family and community characteristics, and social forces.

CONDUCT OF SCIENCE

In the coming years, biomedical and biobehavioral researchers will need to work as transdisciplinary teams, manage massive amounts of data, and acquire new and diverse skill sets. The very breadth of NICHD's mission requires us to create, train, and support such teams to be able to fully translate our research advances into actions that improve the health of women, children, families, and individuals with disabilities.

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

Mr. Chairman and members of the committee: 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 2014 budget of $699,216,000 includes a decrease of $2,191,000 below the comparable fiscal year 2012 level of $701,407,000. 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.

STRATEGIC PLANNING

"The NEI Challenge to Identify Audacious Goals in Vision Research and Blindness Rehabilitation" was a novel strategic planning initiative designed to identify innovative, groundbreaking long-term research goals. The challenge was open to anyone with an idea for a 10-year audacious research goal including scientists, engineers, clinicians, and the public. NEI used a new prize competition authority, from the America COMPETES Reauthorization Act of 2010, to attract attention and received more than 500 ideas for audacious goals. A Federal review panel selected 10 winning entries for further consideration. Then, more than 200 leading scientists and clinicians met to further develop these ideas at the NEI Audacious Goals Development Meeting held in February 2013. Afterwards, NEI announced an audacious goal (Regenerate Neurons and Neural Connections in the Eye and Visual System) and two high-priority areas (Molecular Therapy for Eye Disease and the Intersection of Aging and Biological Mechanisms of Eye Disease) at the Association for Research in Vision and Ophthalmology meeting on May 5. NEI is now identifying the necessary steps to boldly attack these research endeavors over the coming decade.

CLINICAL TRIALS

This month, NEI-supported investigators published results of the Age-Related Eye Disease Study 2 (AREDS2), a large, multi-center clinical trial designed to refine the antioxidant and mineral supplement formulation that was evaluated in the original AREDS clinical trial. The original Age-related Eye Disease Study (AREDS) established that daily doses of vitamins C and E, beta-carotene, zinc, and copper slows the progression to advanced age-related macular degeneration (AMD), the leading

cause of visual impairment and legal blindness in older Americans. AREDS2 was undertaken for three reasons. First, preliminary evidence indicated that Omega-3 fatty acids might be beneficial. Second, beta-carotene, used in AREDS, was found to increase lung cancer risk in cigarette smokers. Third, it was suggested that the rather high zinc level in AREDS might cause minor side effects, such as stomach upset. AREDS2 investigators found that adding Omega-3 fatty acids, replacing beta-carotene with two other carotenoids, lutein and zeaxanthin, and lowering zinc levels maintained, but did not improve the effectiveness of the original formulation. Thus, changing the carotenoid and lowering the zinc in original AREDS formulations offers an equally effective alternative with fewer side effects. The AREDS2 study results provide physicians and patients with new information about delaying or preventing vision loss from AMD.

In February 2013, the FDA approved the Argus II Retinal Prosthesis System, a medical device capable of restoring ambulatory vision to those blind from retinitis pigmentosa. Argus II consists of a miniature video camera that is mounted on a pair of glasses. A processing unit worn on a belt converts images captured by the camera into electrical impulses that are wirelessly transmitted to a 60-electrode grid implanted in the eye. Users perceive the electrical impulses as patterns of light that produce visual information. The Argus II, developed by Second Sight, Inc., was made possible through more than a decade of clinical trial support from NEI.

TRANSLATIONAL RESEARCH

Retinitis pigmentosa (RP) is a group of rare, degenerative diseases that result from mutations in any one of 40 genes that function in rod photoreceptor cells in the retina. These cells form our peripheral vision and allow us to see in dim and dark environments. As RP progresses, patients experience night blindness and severely restricted visual fields. For reasons that are not understood, the loss of rods eventually leads to the degeneration and death of cones, the photoreceptor cells in the central portion of the retina that allow us to perceive fine visual detail and color. Without central vision, it is impossible to perform essential tasks of daily life such as reading, driving, walking without assistance, or recognizing faces and objects.

Vision researchers have long sought a therapeutic approach that can address multiple RP genotypes. However, current efforts with gene therapy address only one specific gene defect at a time. In a highly novel approach that could be applied to most, if not all, forms of RP, NEI-supported investigators genetically reprogrammed rods to become cone-like cells in a rodent model of RP. This approach reduced rod cell function but preserved cone cells. Although such a treatment would leave patients with limited peripheral vision and night blindness, this would be preferable to the added debilitating loss of central vision for the estimated 200,000 Americans who live with RP.

NEI-supported investigators have developed a potential new treatment to prevent proliferative vitreoretinopathy (PVR) a sight-threatening complication of retinal detachment that requires prompt surgical treatment. PVR occurs in about 10 percent of retinal detachments, resulting in permanent scarring of the retina. In this condition, retinal pigment epithelial (RPE) cells, which line the neural retina, migrate through the retinal detachment into the vitreous fluid where they rapidly multiply, dedifferentiate and contribute to the formation of an abnormal membrane on the surface of the retina. This membrane eventually contracts, pulling at the retina and forming a larger detachment. PVR causes heavy scarring of the retina and severe visual impairment. NEI investigators identified seven classes of biological growth factors and regulatory proteins that promote the proliferation and contraction of the RPE-derived membrane in an animal model of PVR. By inhibiting the expression of these biological factors, the investigators prevented PVR. This study provides insight into the causes of PVR and proof-of-concept for treating the condition.

The cornea, the outer protective layer of the eye, is amazingly resilient to infection. By exposing cultured human corneal cells to bacteria, NEI researchers identified a class of peptides important in the cornea's defense against bacterial infection. Blocking these peptides in a rodent model led to a marked increase in corneal infections. Synthetic variations of these peptides effectively killed bacteria that lead to flesh-eating disease and strep throat, staph infections, diarrhea, and cystic fibrosis associated lung infections. The findings could lead to a powerful new class of low-cost antibiotics at a time when antibiotic resistance to existing agents is of growing concern.

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 committee: 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 2014 NIEHS budget of $691,348,000 includes an increase of $7,051,000 from the comparable fiscal year 2012 level of $684,297,000.

INTRODUCTION

In fiscally challenging times for science, NIEHS is finding innovative ways to maximize its investments through strategic planning, collaborative research, and focused translation of science. For example, NIEHS grantees have discovered a key mechanism by which dietary omega-3 fatty acids (fish oils) could reduce the growth and spread of cancer, which kills 580,000 Americans a year.[1] New findings from the NIEHS Sister Study show that even moderate physical activity can reduce breast cancer risk,[2] and that estrogen may help offset effects of obesity and alcohol on risk.[3]

COLLABORATIVE RESEARCH

NIEHS develops and leads multi-disciplinary collaborations in areas such as the Gulf Oil spill, breast cancer and the environment, nanotechnology, bisphenol A, and science data management. In partnership with the Substance Abuse and Mental Health Services Administration, the NIEHS Gulf Long-term Follow-up (GuLF) Study of 33,000 men and women will assess mental health trajectories, resiliency and coping, and mental healthcare needs of participants. NIEHS has invested $30 million from 2009 to date working with Federal partners and the Nation's leading researchers to fill data gaps and resolve controversies over the human health effects of exposure to low levels of BPA. Nearly 150 papers have resulted from this effort so far.[4] Recent observational human studies[5] show that early life exposures to BPA can potentially lead to diseases or health problems in adulthood such as prostate and breast cancer, obesity, diabetes, and cardiovascular, neurobehavioral, and reproductive disorders. Work of the Engineered Nanomaterials Grand Opportunity (Nano GO) Consortium of 13 laboratories now provides investigators with standardized methods for predicting the toxicity of selected nanomaterials.[6 7] NIEHS is a partner in the new National Consortium for Data Science that aims to address the challenges of collecting, sharing, and using large, diverse datasets. At its recent summit, genomic and data scientists drafted recommendations for translating genomic data into better, more affordable healthcare by developing new ways to collect, manage, analyze, and apply massive amounts of data into tools for scientific discovery and economic growth.

SCIENTIFIC ADVANCES

NIEHS's investigator-initiated research provides critical advances in environmental health and basic sciences. New findings suggest that Vitamin D may reduce

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the risk of uterine fibroids,[8] a condition that, according to NIH, afflicts up to 80 percent of American women, causes more than 200,000 hysterectomies each year, and results in direct health costs of $2.1 billion. A recent study points to exposure to polybrominated diphenyl ethers in flame retardants as a factor in increased risk of Parkinson's disease.[9] A new analysis of the scientific literature shows that exposure to increased levels of particulate matter during pregnancy can lead to greater risk of low birth weight babies,[10] putting them at risk of poor health in childhood and adulthood.

Exposure to toxic substances in the environment accrues huge costs in human suffering, and results in economic costs to individuals and society; NIEHS-funded studies illustrate this dual burden. Each year in Europe, 1.8 million children suffer unsafe prenatal methylmercury exposures that affect brain development, mostly from fish in mothers' diets. Preventing such exposures could save the European Union 8 to 9 billion euros per year in lost earning potential of these children.[11] In a study of approximately 12.5 million elderly Medicare beneficiaries, researchers found a consistent increase in costly respiratory hospitalizations with increasing outdoor temperatures.[12]

STAKEHOLDER TRANSLATION

Just as scientific rigor is required to generate sound research findings, vigorous approaches are needed to translate these findings to stakeholders. In 2012, NIEHS released a strategic plan that identifies key goals for the next 5 years that will provide the rubric for NIEHS to achieve its vision as a catalyst for the application of state-of-the-art biomedical research to the most critical environmental health problems. NIEHS "talks the talk" by committing to effective research translation in its strategic plan, and "walks the walk" through engagement and translation activities with the American public.

Community Forums around the United States allow the public to raise environmental health concerns with the NIEHS director. In November 2012, NIEHS held its first virtual Community Forum on environmental exposures and childhood obesity, using social media and webcasting to reach 600 viewers and spark 1.5 million tweets. In a March forum in Seattle, residents voiced concerns about a site along the Duwamish River that is one of the most polluted in the U.S., as well as home to low-income and recent immigrants, and fishing grounds of three Northwest Tribes. In February, the NIEHS-led Interagency Breast Cancer and Environmental Research Coordinating Committee released "Prioritizing Prevention," recommendations for reducing environmental exposures and modifying lifestyle factors implicated in breast cancer.

NIEHS provides critical Federal and global leadership to advance science on how the environment affects people's health to promote healthier lives.

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 committee: 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 2014 NIAMS budget of $540,993,000 includes an increase of $6,202,000 over the comparable fiscal year 2012 level of $534,791,000.

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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. The burden of these diseases is substantial. Arthritis limits the activities of nearly 21 million adults in the United States each year; medical care and lost wages attributable to musculoskeletal conditions cost Americans an estimated $950 billion annually; and skin conditions such as eczema and psoriasis affect more than 12 percent of people world-wide.[1] NIAMS is accomplishing its mission of improving health by supporting basic and translational research that will impact clinical practice, by training the next generation of bone, joint, muscle, and skin scientists, and by disseminating the findings from its studies, and related health information, to all Americans.

BASIC SCIENCE: THE FOUNDATION FOR TOMORROW

Tomorrow's treatments are rooted in the basic research conducted today. NIAMS is committed to better understanding the molecular and cellular processes that contribute to health and disease. This basic research will serve as the foundation for new diagnostic tests, therapies, and prevention strategies that will improve the lives of those who are affected by arthritis, and musculoskeletal and skin conditions.

NIAMS investigators are leveraging the Nation's investment in understanding the human genome and making use of its associated technologies. One such project is studying facioscapulohumeral muscular dystrophy (FSHD)—a neuromuscular disease of the face, shoulders, and upper arms. Building on earlier findings about DNA sequences on chromosome 4 that lead to FSHD, researchers discovered that a rare form of the disease—called FSHD2—is caused by mutations on both chromosome 4 and chromosome 18. These results set the stage for new diagnostic tests and treatments for patients who have FSHD2. Moreover, the recognition that distant genes interact with each other may lead to similar discoveries in other conditions.

NIAMS recognizes industry's important role in conducting basic research, developing new technologies, and commercializing federally supported discoveries. For this reason, NIAMS is offering grants to eligible small businesses for development of biomarkers or therapies for rare musculoskeletal, rheumatic, or skin diseases.

TRANSLATIONAL SCIENCE: BRIDGING BENCH AND BEDSIDE

NIAMS basic research can only improve public health when the understanding it generates is translated into new and improved treatments and preventive strategies. Recent insights into the molecular mechanisms of cell processes are already suggesting treatments. NIAMS researchers at the NIH Clinical Center launched a small clinical trial after experiments into the cause of neonatal-onset multisystem inflammatory disease (NOMID) revealed that it may be corrected with the adult rheumatoid arthritis (RA) drug anakinra. The children participating in the trial, who had been ill for years, improved within days of receiving the drug. Their rashes disappeared, their eye problems resolved, and their hearing improved or stopped worsening. The investigators then initiated a 5-year study, which led to U.S. Food and Drug Administration (FDA) approval of anakinra for pediatric NOMID patients earlier this year.

NIAMS-funded basic research also contributed to the recent FDA approval of a new treatment for RA. The drug, tofacitinib, targets a protein discovered at NIH in 1993. Following many years of collaboration between NIH and private industry, tofacitinib became the first drug approved in more than a decade that can be taken as a pill, rather than an injection, to slow or halt RA joint damage. It provides an option for adults with moderately to severely active RA who do not respond well to the standard therapy for the disease—methotrexate.

In addition to helping patients by supporting basic research and developing new treatments, NIAMS facilitates work that guides clinicians in the use of existing therapies. NIAMS funding assisted a national consortium of pediatric

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rheumatologists establish treatment recommendations for newly diagnosed juvenile idiopathic arthritis patients, and for children who develop kidney inflammation due to lupus. These recommendations are guiding patient care today and can be integrated into future effectiveness and toxicity studies as therapies are developed.

Other work may help clinicians predict which scleroderma patients will respond to the drug mycophenolate mofetile (MMF), one of the standard therapies for this disorder. A small clinical trial built on findings about the molecular causes of scleroderma revealed a connection between gene expression patterns in patients' skin biopsies and their responses to MMF. If an ongoing study confirms this genetic biomarker's predictive value, countless patients might be spared needless exposure to MMF and could begin receiving other drugs before their disease progresses.

NIAMS-supported research also is contributing to knowledge about dietary and behavioral changes that can prevent common public health challenges. Poor nutritional habits increase older Americans' risk of metabolic acidosis, a condition that occurs when the body produces too much acid or the kidneys fail to remove excess acid from the blood. Because bone is a reservoir for alkaline salts (e.g., calcium phosphate), it can lose minerals and weaken in an effort to maintain a healthy acid-base balance. Findings from an NIAMS-funded clinical trial revealed that the dietary supplement potassium citrate improves the acid-base equilibrium of people's blood, their calcium balance, and markers of skeletal health. This supports the hypothesis that potassium citrate can slow or prevent bone loss that occurs with age. If future studies confirm the results, potassium citrate could become a safe and easily administered intervention for patients who have, or are at risk of, osteoporosis and related fractures.

NIAMS research findings are assisting healthcare providers and patients select among treatment options. Many adults have debilitating knee pain due to a tear in the meniscus, a cushion-like tissue that absorbs impact. Although meniscal tears can be treated with physical therapy or surgery, it was unclear which intervention was best until a recent paper showed that most patients benefited equally from either option over time. Those in the physical therapy group improved less quickly, however, and about one-third resorted to surgery because physical therapy did not provide adequate relief.

ENSURING A DIVERSE SCIENTIFIC WORKFORCE

NIAMS is committed to developing and retaining a diverse and collaborative scientific workforce. Planning discussions in fiscal year 2012 that included investigators, health professionals, and patients identified the transition from mentored research to full independence as a vulnerable period in clinician-scientists' careers. In fiscal year 2013, NIAMS met with grantees nearing the end of their clinical or patient-oriented research career development awards to learn about the challenges they and their peers are facing. NIAMS plans for fiscal year 2014 include a similar effort, with a long-term goal of identifying ways to better support early-stage investigators' transition to research independence.

SHARING HEALTH INFORMATION AND RESEARCH PROGRESS

The Internet and other electronic communication platforms have emerged as valuable tools for disseminating health information. An increasing number of visitors are accessing the NIAMS Web site from mobile devices, and current trends indicate that mobile traffic to Web sites may overtake desktop traffic as soon as 2015. In response, NIAMS began providing its health information in a mobile device friendly format in fiscal year 2013. NIAMS will continue to assess and adapt to new technologies and tools to provide research updates and health information to the widest possible audience.

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 committee: 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 2014 NIDCD budget of $422,936,000 includes an increase of $7,436,000 over the comparable fiscal year 2012 appropriation of $415,500,000.

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 on communication disorders.

RESEARCHERS RESTORE HEARING IN NOISE-DEAFENED MICE

Our ability to hear relies on sensory hair cells in the inner ear. The hairs on these specialized cells convert sound vibrations into electrical signals, which travel to the brain by way of the auditory nerve. When hair cells are damaged—by disease, injury, or aging—a person experiences hearing loss, and mammals cannot regenerate these lost hair cells.

Researchers supported by NIDCD have shown for the first time that a drug can be used to grow sensory hair cells in the inner ear. They injected a drug into the cochlea (a spiral shaped organ in the inner ear that shelters hair cells) of mice made deaf by exposure to loud noise. The drug blocked a cell-signaling system known to keep stem cells in the inner ear from turning into hair cells. By blocking that particular pathway, the drug encouraged cells supporting and surrounding the hair cells to turn into new hair cells, which led to a small improvement in the mice's hearing.

This is the first study to show that scientists can use a drug to restore partial hearing in a mouse with noise-induced hearing loss. Scientists now hope to develop similar treatments to reverse hearing loss in humans, especially among the estimated 36 million adult Americans who report hearing loss.

NOVEL APPROACHES OF INNER EAR REGENERATIVE THERAPIES

Although research to determine ways to regenerate inner ear hair cells is under way, there remains a lack of potential treatments to restore lost mammalian hair cell function. Research is needed to identify and facilitate important molecular switches and regulators that initiate and sustain mammalian hair cell repair.

NIDCD places a high priority in research that focuses on regenerative medicine. For example, the Institute is planning a research initiative for fiscal year 2014 with the goal of developing hair cell regeneration strategies. NIDCD held a workshop, in September 2011, to identify opportunities to induce regeneration in the inner ear. As a result of this workshop, NIDCD issued a Funding Opportunity Announcement to encourage innovative and novel approaches to inner ear regenerative therapies research. The ultimate goal of the research is to identify and "turn on" important molecular switches and regulators to enable mammals to regenerate and repair their own inner ear hair cells. This research may result in therapies that will provide hope of future treatments for those who have lost hearing due to aging, injury, or noise exposure, including military veterans returning from active duty.

Another purpose of the initiative is to attract and support NIH-defined basic and clinical early-stage investigators (ESIs) to the area of biological repair of mammalian inner ear hair cells. NIDCD is especially interested in ESIs who bring new, innovative approaches, and strategies from scientific fields minimally represented in the NIDCD portfolio, such as tissue fabrication, biomaterials, and regenerative medicine. By supporting ESIs from other scientific areas, this initiative will encourage diversified approaches and an increased number of investigators focused on regenerative therapies in the inner ear.

RESEARCHERS IDENTIFY GENE LINKED TO PROGRESSIVE HEARING LOSS FROM NOISE AND AGING

An international team of scientists funded by NIDCD has identified the first gene in humans and mouse models that is associated with both noise-induced and age-related hearing loss. The gene, P2X2, appears to be crucial for the preservation of life-long normal hearing and for protection from exposure to loud noise. P2X2 is associated with the human gene locus DFNA41, a form of hearing loss that typically begins early in life (around 12–20 years of age), and progresses with age. High-frequency tinnitus (high-pitched ringing in the ears) often accompanies hearing loss associated with DFNA41.

The research team discovered that the P2X2 gene mutation found in DFNA41 results in defects in sensory hair cells in the inner ear, which eventually lead to ongoing hearing loss. The study establishes, at the cellular and molecular levels, that the function of this ion channel, previously known to be involved in sensory signaling of pain, has a major impact on noise-induced and age-related hearing loss.

These findings demonstrate the importance of genetic approaches to uncover the underlying mechanisms that contribute to hearing loss, either as a result of age or

chronic exposure to noise. Importantly, identifying the P2X2 mutation may provide scientists with a way to develop targeted treatments for progressing hearing loss in humans with DFNA41, and may be applicable to the treatment of noise-induced and age-related hearing loss in the broader population.

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS SUPPORTS RESEARCH TO DEVELOP A VACCINE AGAINST AN EMERGING TYPE OF CHILDHOOD EAR INFECTION

Ear infections during childhood are of great concern to NIDCD, because they not only cause pain and suffering, but they also interfere with a child's ability to hear properly during a critical period of language development. Since 2000, childhood vaccines have prevented many ear infections caused by two strains of bacteria—"Haemophilus influenzae and pneumococcus". However, doctors are now seeing an increase in the number of ear infections caused by another strain of bacteria, called "Moraxella catarrhalis (M. catarrhalis)".

NIDCD-supported scientists are working to understand how this bacterium infects humans and avoids destruction by the immune system. They hope to identify a particular structure (called an antigen) that is very similar among all strains of "M. catarrhalis", so that a vaccine based on a single antigen will protect against as many strains of the bacterium as possible.

The research team is using bioinformatics to predict which "M. catarrhalis" proteins are likely to be found on the surface, to make an attractive antigen target. They are using gene chips to identify which genes are identical or similar among multiple strains of the bacterium, and then testing these in petri dishes and in animal models. The scientists are now testing several promising vaccine antigens against "M. catarrhalis", and hope that a new vaccine could be ready for human testing in a few years.

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

Mr. Chairman and members of the committee: 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 2014 budget of $1,071,612,000 includes an increase of $20,202,000 over the comparable fiscal year 2012 level of $1,051,410,000.

The individual and societal impact of both licit and illicit substance abuse in America is incalculable, not to mention the associated economic cost, estimated at well over half a trillion dollars a year in healthcare, crime-related, and productivity losses. The current landscape of the problem reveals both new and recurrent trends. Prescription drug abuse remains at high levels in all age groups, causing thousands of needless overdose deaths each year. New synthetic drugs, like "bath salts" and synthetic marijuana ("spice"), are sending many teens and young adults to emergency rooms. And as cultural changes promote greater acceptance of the use of marijuana, more teens report using it and fewer perceive its real risks. This, despite new research showing that early onset of marijuana use can disrupt learning circuitry and lower IQ.

NIDA supports a broad research agenda that leverages the full potential of genetic/epigenetic, psychosocial, neuroimaging, pharmacological, health services, and epidemiological studies in order to reduce the burden of drug abuse and addiction. In the context of the current prescription drug abuse epidemic, for example, NIDA is harnessing the translational power of a multidisciplinary addiction science to: (1) identify the major factors that modulate risk; (2) develop universal, broad-based prevention and treatment models involving individuals, their families, schools, and communities; (3) develop pain medications with little or no abuse potential (for example, a new opioid medication that must pass through the digestive system to become active, preventing its abuse via non-oral routes); and (4) promoting physician education to both improve pain treatment and minimize drug abuse. NIDA also supports research to make the most of new opportunities and therapeutics, including healthcare reform legislation that stands to extend effective interventions to underserved populations, including people with substance use disorders.

NOVEL THERAPEUTICS

To help those already suffering from addiction, we must expand our treatment toolkit. NIDA is optimally positioned to parlay research findings into new medication targets and promising compounds for pharmaceutical company investment or

partnerships. Strategies now being tested include recruiting the body's immune system to attack and destroy drug molecules before they can enter the brain. This is being tried against nicotine, heroin, and stimulant drugs such as cocaine and methamphetamine, for which no medications are yet available. A related strategy involves delivery of an enzyme that has been molecularly engineered to rapidly destroy cocaine in the blood, currently in a phase II clinical trial. Combining existing medications is another promising approach, which has proven successful for a number of diseases (e.g., cancer and HIV/AIDS) but has not been exploited for treating addictive disorders. NIDA also continues to use its National Drug Abuse Treatment Clinical Trials Network (CTN) as a community-based platform to test new therapeutic interventions. For example, the CTN is testing an FDA-approved anxiety medication, buspirone, for its safety and efficacy in preventing relapse to cocaine use.

WIDENING THE SCOPE OF CARE

Even effective interventions are not useful if they fail to reach the people who need them. Implementation research and inclusiveness of diverse populations in clinical trials are thus vital components of NIDA's research agenda to close the vast treatment gap. One example is research that pertains to the integration of substance abuse screening, brief intervention, and referral to treatment (SBIRT) into routine medical care and evaluation of the impact of such an approach in clinical outcomes of patients. Importantly, our goals in this context dovetail those of the Affordable Care Act, which promises to expand the scope of care and treat more patients suffering from substance use disorders. Another critical setting is the criminal justice system, where NIDA has long supported research to better deliver evidence-based treatment. Now, this focus extends to youth in the juvenile justice system, virtually all of whom could benefit from prevention or treatment interventions for drug abuse.

Improving drug abuse prevention and treatment services also helps ameliorate other health consequences of abuse, including infectious diseases like HIV and hepatitis C virus (HCV) that can readily spread through the sharing of needles and other injection drug use equipment. One of the many translational initiatives spearheaded by NIDA is the "Seek, Test, and Treat" (and "Retain") strategy, aimed at evaluating the impact of expanding highly active antiretroviral therapy (HAART) coverage in criminal justice and other at-risk populations through aggressive outreach, early entry into HIV treatment, and follow-up in the community. There is accumulating evidence that early treatment with HAART reduces new HIV diagnoses, deaths, and HIV prevalence, suggesting that "Treatment as Prevention" should be implemented as soon and as widely as possible.

NEW SCIENTIFIC OPPORTUNITIES

By taking full advantage of continuous developments in a wide range of scientific disciplines, NIDA is positioned to make significant advances in averting and treating addictive disorders. For example, we can now affordably sequence full individual genomes to identify rare genetic variations that influence addiction and responses to treatment, increasing not just our basic understanding of addiction but also paving the way for personalized treatments. Through the rapidly developing field of "epigenetics", we can determine the lasting impact of environmental variables like early stress or drug exposure on gene expression linked to later drug use. Another powerful new tool called "optogenetics", which allows us to activate (or deactivate) specific brain cells and networks, has enabled NIDA researchers to link compulsive cocaine-seeking in rats to deficits in the prefrontal cortex that were reversed by activating the affected brain regions. Clinical trials will soon test whether noninvasive (magnetic) stimulation can modify brain activity and reduce compulsive drug-seeking and craving in human drug users. Meanwhile, advanced imaging techniques are allowing us to ask questions about brain structure and function that were unimaginable just a few years back.

Yet even with these new technologies, the underlying causes of most neurological and psychiatric conditions remain poorly understood, due to the human brain's incredible complexity. NIDA is one of the key participants in an exciting new NIH initiative to conquer this major frontier. Brain Research through Advancing Innovative Neurotechnologies, or BRAIN, will produce a revolutionary new dynamic picture of the brain, showing how individual cells and complex neural circuits interact in healthy individuals, and in those with brain disorders.

To better capitalize on synergies in addiction science, NIDA, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Cancer Institute (NCI) have formed a consortium, the Collaborative Research on Addiction at NIH

(CRAN), which will pool resources and expertise to address unmet research opportunities and public health needs. Among these, the study of "comorbidities" is poised to benefit. NIDA, NIAAA, and the National Center for Complementary and Alternative Medicine, in collaboration with the Department of Defense, recently issued a call for research on interventions to prevent comorbid alcohol and other drug abuse in U.S. military personnel, veterans, and their families. NIAAA and NIDA also issued a call for research on mechanisms of alcohol and nicotine co-addiction.

The accelerating pace of science is rapidly outstripping our capacity to use what we collect. "Big Data" requires a significant repositioning in who we train and how we can best identify and exploit emerging scientific opportunities. We will need to build a workforce that includes people skilled in non-biomedical fields, such as informatics, computational science, mathematics, and engineering. Training the next generation of scientists to be able to understand the possibilities and complexities of what they will be dealing with is a daunting but exciting challenge as we go forward.

In closing, we know much more about the causes and treatment of substance use disorders than ever before. Yet obstacles such as the lingering stigma attached to diseases of addiction continue to hamper our ability to recognize and care for those afflicted. NIDA remains committed to tackle these and other challenges, taking advantage of unprecedented scientific opportunities to transform how we prevent and treat substance abuse and related health consequences in this country.

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

Mr. Chairman and members of the committee: 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 2014 NIAAA budget request of $463,848,000 reflects an increase of $5,183,000 over the comparable fiscal year 2012 level of $458,665,000.

SCOPE OF THE PROBLEM

According to the Centers for Disease Control and Prevention, excessive alcohol use cost the U.S. an estimated $223.5 billion in 2006; it also takes a tremendous toll on individuals and their families. Alcohol affects individuals across the lifespan, from the developing fetus to the elderly. Each of you likely knows someone affected by alcohol problems.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM RESEARCH

To reduce the considerable burden of illness associated with alcohol misuse, NIAAA is working to prevent the onset and escalation of drinking during childhood and adolescence and intervene with problem alcohol use at all ages. A substantial portion of NIAAA's research portfolio focuses on the underlying mechanisms, prevention, and treatment of alcohol dependence. The remainder is allocated to studies on the consequences of alcohol use, including: health benefits associated with moderate drinking; adverse effects resulting from alcohol misuse such as fetal alcohol spectrum disorders (FASD), effects on the developing adolescent brain, and tissue and organ damage; and policy research to reduce harms both to drinkers and those around them.

FUNCTIONAL INTEGRATION

NIAAA has embraced the decision of the NIH Director to pursue a functional integration of addictions research, which provides a framework for NIAAA, the National Institute on Drug Abuse (NIDA), the National Cancer Institute (NCI), as well as other Institutes and Centers (ICs), to enhance and expand collaborations and identify synergistic research opportunities to advance addictions science. Now referred to as the Collaborative Research on Addictions at NIH (CRAN), this new venture will support a variety of activities. Importantly, while advancing addictions research, a functional integration maintains the unique research contributions of each IC.

Prior to the official launch of CRAN, NIAAA, and NIDA implemented a number of changes to improve integration between the two ICs and initiated additional joint funding opportunity announcements (FOA). One joint FOA focuses on research to prevent alcohol and other drug abuse in active military personnel, veterans and their families. Going forward, CRAN will explore cross-cutting research opportunities such as studies on individuals who suffer from addiction to multiple sub-

stances—40 percent of individuals who have a past year addiction to illicit drugs and/or abuse prescription drugs also have past year alcohol abuse or dependence, and 16 percent of individuals with past year alcohol abuse or dependence have a past year drug addiction. CRAN will also support efforts to identify mechanisms that underlie tobacco, alcohol and/or other drug addiction, recognizing that while some mechanisms may be common to more than one substance, others will be unique. Expanding studies to address multiple substances when feasible and appropriate will enhance our ability to treat multi-substance co-morbidities in an efficient and cost-effective manner. Funding opportunities under CRAN will begin in fiscal year 2014 with two initiatives; the first will expand existing projects to be more integrative and/or collaborative, the second will focus on mobile technologies and social media for interventions for substance abuse.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM'S UNIQUE RESEARCH FOCUS

NIAAA also has a robust research program outside of CRAN. Studies exploring pharmacological, behavioral and policy interventions to reduce acute and chronic consequences of alcohol misuse are a major component of NIAAA's portfolio. Medications development is an active area of study, both for the treatment of alcohol dependence and for the treatment of consequences of chronic alcohol misuse such as alcohol-induced liver disease. NIAAA's Clinical Investigations Group (NCIG) has streamlined the process for phase 2 clinical testing of potential compounds for alcohol dependence and has established an active collaboration with pharmaceutical companies. In a recent NCIG-led study, the smoking-cessation medication varenicline (Chantix®) significantly reduced alcohol consumption and craving among people who are alcohol-dependent. Varenicline's effects were comparable to those seen in studies of naltrexone and acamprosate, two of the medications already approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol dependence. If varenicline receives FDA approval for treatment of alcohol dependence, it could significantly expand treatment options. Personalizing treatment also continues to be a goal, and studies showing links between an individual's genetic make-up and treatment efficacy for various medications suggest that goal is within reach. Relapse, however, is still common and a focus of NIAAA research. A recent study showed that distinct patterns of brain activity are linked to a higher rate of relapse among patients in early recovery. These patterns may be useful for identifying patients at greatest risk for relapse.

The link between stress and alcohol-related problems is an important area of investigation. While a number of studies have focused on how stress contributes to the development of alcohol-related problems and relapse, a recent line of investigation is exploring how chronic alcohol use might increase vulnerability of the brain to the development of stress-related disorders. A study in mice suggests that chronic alcohol use may increase the risk for post-traumatic stress disorder (PTSD) by altering neural circuits that normally enable the brain to extinguish fear following a traumatic event.

NIAAA also continues to support medications development for the treatment of alcoholic liver disease (ALD), one of the most serious medical consequences of alcohol dependence, and continues to seek biomarkers for alcoholic liver damage. Scientists are gaining an appreciation for the interconnectedness of systems within the human body. NIAAA uses a systems biology approach to investigate how pathological changes in one organ as a result of alcohol exposure can also result in physiological aberrations in another. Basic research using animal models is also important to better understand the mechanisms underlying ALD; however, many of the current models do not evoke the full range of symptoms or are expensive and technically difficult. A new mouse model of alcohol drinking and disease was developed which more closely approximates ALD in humans and may also be useful to study alcohol damage of other organs.

The developing embryo/fetus is uniquely vulnerable to the effects of alcohol; prenatal alcohol exposure is a significant contributor to neurodevelopmental disorders in children. Understanding the mechanisms leading to the neurodegeneration that underlies development of FASD is a critical step in developing treatments. A recent study provides evidence that endocannabinoids and their receptors in the brain play a role in the development of FASD.

Policy research is another important component of NIAAA's portfolio. Data from NIAAA-supported studies will help inform local decisions such as the implementation of policy measures on college campuses to reduce alcohol poisonings. In addition, research findings play an important role in national issues such as the debate over the legal limit for blood alcohol content for operation of a motor vehicle, as policy-makers work to find a balance between increased alcohol restrictions and public

safety. Screening and brief intervention for harmful alcohol use have been a major focus of NIAAA research for several decades. Based on this research, the U.S. Preventive Services Task Force (USPSTF) recently recommended that clinicians screen adults for alcohol misuse and provide persons engaged in risky or hazardous drinking with brief interventions. The USPSTF did not endorse screening for adolescents citing insufficient evidence. To increase this evidence base, NIAAA is supporting six studies to evaluate its youth alcohol screening guide in a variety of settings as a predictor of alcohol risk, alcohol use, and alcohol problems, and as an initial screen for other behavioral health problems such as drug use or smoking.

In summary, NIAAA is enthusiastic about opportunities to expand research to improve the lives of Americans struggling with addiction to alcohol and other substances through the newly created CRAN. At the same time, NIAAA continues to focus on reducing the significant burden of illness associated with alcohol misuse.

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

Mr. Chairman and members of the committee: I am pleased to present the President's budget request for the National Institute of Nursing Research (NINR) of the National Institutes of Health (NIH). The fiscal year 2014 NINR budget of $146,244,000 includes an increase of $1,744,000 over the comparable fiscal year 2012 level of $144,500,000.

The mission of NINR is to promote and improve the health of individuals, families, communities, and populations. The Institute does so by supporting and conducting clinical and basic research to build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms of illness, improve palliative and end of life care, and train the next generation of nurse scientists. NINR-supported investigators contribute to developing the evidence base for science-driven practice through innovative treatment and behavioral research. Today, I offer a brief overview of NINR's investment and progress in six key areas and provide examples of how the research we support improves quality of life.

SYMPTOM MANAGEMENT IN MULTIPLE CHRONIC CONDITIONS

Due to the large aging population with longer life expectancies, and treatment advances for formerly fatal diseases, over one in four Americans are living with multiple chronic conditions (MCC) and their associated adverse symptoms. To address these symptoms and improve quality of life, NINR currently supports five Centers of Excellence in symptom science that explore pain, sleep disturbance, and the effects of chronic illness on neurocognitive functioning. A recent NINR-supported study found an association between an anti-inflammatory protein and a symptom cluster, including pain, fatigue, and sleep disturbance, opening the door to potential therapeutics development to alleviate these symptoms.

FAMILY AND COMMUNITY-BASED RESEARCH

The family and community-based approach to clinical and translational research is intrinsic to nursing science and NINR. Child behavioral issues can create problems that negatively affect learning and peer relationships. NINR-supported studies that developed and tested the Chicago Parent Program (CPP), a high-quality, cost-effective, early childcare program for low-income communities that promotes positive parenting behaviors and reduces risky behaviors in children and their families. The CPP was adapted and disseminated to Chicago Head Start sites, where it was well-received in the community. The researchers reported improvements in parenting skills and child behavior. Based on these results, CPP-derived interventions have been implemented in diverse settings across the U.S., such as the Mayo Clinic, the Harlem Children's Zone, Johns Hopkins Bayview Medical Center, and New York City and Chicago Head Start centers. CPP's successful adoption into diverse communities underscores the importance of partnering with individuals, families, communities, and healthcare practitioners to ensure a program's effective translation into real world settings.

PALLIATIVE CARE AND END OF LIFE RESEARCH

As the lead NIH Institute for end-of-life research, NINR supports evidence-based palliative care research that assists individuals, families, and healthcare professionals in managing the symptoms of advanced illness and planning for end-of-life decisions. Individuals of all ages with advanced illness can face protracted courses of decline, requiring that difficult decisions be made to ensure appropriate interven-

tion and to maximize quality of life. NINR supports a palliative care research cooperative to enhance the evidence base for palliative care by carrying out multi-site research studies and clinical trials to be used to inform health practice and policy.

NINR grantees are also evaluating palliative care interventions for patients with heart failure. Others are testing the efficacy of an integrated model of palliative care early in the cancer diagnosis process. The Institute also supports research on family members' perceptions and the importance of end-of-life strategies. These activities will provide for both optimal care and treatment for patients facing life-limiting conditions, and assist patients and family members.

RESEARCH TO IMPROVE CLINICAL PRACTICE

As the healthcare providers most frequently interacting with patients, nurses are uniquely positioned to develop successful interventions to address treatment challenges. As our Nation's aging population continues to grow, the demand for critical care services is projected to increase. As a result, the number of patients transferred to long-term acute care hospitals, and the resulting costs, are expected to increase significantly. A recent NINR-funded study compared two methods for weaning patients from prolonged mechanical ventilation. Researchers found that one method, using a device known as a tracheostomy collar, resulted in earlier, successful weaning from mechanical ventilation. Implementing standard, best practice guidelines based on these findings could lead to shorter length of stays, better patient outcomes, and decreased healthcare costs. NINR will continue to facilitate the implementation of evidence-based treatment interventions into the clinical setting.

INNOVATIVE TECHNOLOGIES TO ENHANCE HEALTHCARE

Innovative technologies are gaining a larger role in healthcare, and nursing science can provide the foundation for developing novel advances that deliver personalized care and real-time information to individuals, families, and communities. For example, subtle changes in an individual's health status often indicate the early development of acute illness or worsening of chronic conditions, but detecting these changes can be difficult. NINR supported the development of an unobtrusive, inexpensive proactive disease management system that uses infrared sensors to monitor older adults' daily activities and automatically alert healthcare providers to changes in the patient's health status. This technology identified health conditions 1–2 weeks earlier than traditional assessment methods and led to improved functional abilities. Based on these successful results, the researchers hope to expand its use to other care facilities.

For example, NINR supports scientists who are using information technology (IT) to assist patients in understanding the medications they are supposed to take and track whether they are actually taking the medications as prescribed. These scientists are developing an Electronic Medical Record (EMR)-based tool (the Medtable), which is now being evaluated for its effectiveness in provider/patient communication and whether it improves medication knowledge, adherence, and health outcomes among chronically ill adults with complex medication regimens.

LOOKING TOWARD THE FUTURE: NURSE SCIENTISTS

This Nation is facing complex healthcare challenges, and nurses and nurse scientists will play a pivotal role in addressing these issues. Since its inception, the training and career development of an innovative and diverse scientific workforce have been fundamental to NINR's mission. NINR supports nurse scientists and promotes earlier entry of nurses into research by providing research fellowships and career development awards. A recent initiative, the Scholars Training for the Advancement of Research (STAR) program, provides additional resources for institutions to support the "fast-track" training of outstanding undergraduate nursing students who are interested in pursuing a Ph.D. NINR training programs produce future nursing school faculty to strengthen the nursing workforce.

In closing, NINR appreciates the opportunity to support science that can significantly improve the health of the Nation. The Institute provides innovative nursing science that becomes the evidence-based practice for clinical care. NINR will continue its mission to improve the quality of life by advancing nursing science to shape the future direction of healthcare.

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

Mr. Chairman and members of the committee: I am pleased to present the fiscal year 2014 President's budget request for the National Human Genome Research Institute (NHGRI). The fiscal year 2014 budget of $517,319,000 includes an increase of $5,061,000 above the comparable fiscal year 2012 level of $512,258,000.

THE LAST DECADE OF GENOMICS HAS CHANGED BIOMEDICAL SCIENCE

This year, we celebrate the tenth anniversary of the completion of the Human Genome Project (HGP). An ambitious scientific endeavor likened to biology's "moon shot," HGP catalyzed profound changes for many areas of biomedical research and beyond. To provide a perspective about these changes, it is illustrative to compare the "state-of-the-art" at the beginning of HGP in 1990, at its completion in 2003, and now. To place these three-time points in a cultural context, in 1990 Americans communicated by phone and fax; in 2003 it was email; and in 2013 it is the tweet.

Just as technology development has transformed routine communications (from the phone call to the tweet), it has been the cornerstone of the Federal investment in genomics. During the HGP, it took 6–8 years of active sequencing and approximately $1 billion to generate that first sequence of the human genome. In 2003, that same feat would have required 3–4 months and $10–50 million. Today, a human genome can be sequenced in approximately 1–2 days for a mere $3–5 thousand. As the time and cost have plummeted, the power of genomic strategies to advance research and the volume of generated genomic data have increased profoundly.

Why is this massive increase in capacity for data generation important? This extraordinary increase in data generation allows us to understand genome structure and function and through this knowledge to learn how genomes contribute to health and disease. For example, in 1990, we knew of approximately 50 genes that, when mutated, caused a human disease; in 2003 that number was almost 1,500; and today, it is nearly 3,000. Further, knowledge about the genomic basis for our responses to medications—an area of science called pharmacogenomics—has also grown steadily. In 1990, only four Food and Drug Administration (FDA)-approved drugs required labels that pointed out the relevance of a patient's genetic makeup for that medication; by 2003, this number had increased to 46; and today, it stands at 106. In fact, genomic contributions to medical research have been so substantial that fully half of the 2012 "Top 10 Medical Breakthroughs" identified by "Time Magazine" [1] reflected genomics accomplishments, and these were in large part supported and/or facilitated by NHGRI's research programs.

Although extraordinary progress has occurred over the past decade, much remains to be learned about the genome's role in biology and disease, and how to translate that knowledge to improve health outcomes. At the conclusion of HGP, we were but at the beginning of an exciting, but long journey to learn how to apply genomic information to improve health.

LEARNING FROM THE DATA DELUGE

A major challenge for genomics research is the handling, analysis, and interpretation of the large volumes of genomic data now routinely generated. Solving this will require innovative infrastructure and novel methodologies. In fiscal year 2014, NHGRI will support pioneering bioinformatics research across its research portfolio, from the use of cloud computing for efforts such as the 1000 Genomes Project to the development of novel clinical bioinformatics tools by the Clinical Sequencing Exploratory Research (CSER) program and the Electronic Medical Records and Genomics (eMERGE) Network, two flagship programs intended to study how to utilize an individual's genomic information in different clinical settings. Additionally, the Institute will provide key leadership within NIH for the Big Data to Knowledge (BD2K) initiative.

Consistent with NHGRI's 2011 strategic plan, the Institute's portfolio spans a continuum from basic research to study genomic structure and function, to translational research to discover the genomic basis for disease, through efforts to use genomics to increase the effectiveness of healthcare. The ENCyclopedia of DNA Elements (ENCODE) project, a key effort to identify the 'functional parts' within the human genome, published a landmark series of papers in 2012 reporting a catalog of functional elements within the human genome. The ENCODE catalog is like a GPS map for the human genome—just as by zooming in on a GPS map of the United States (to find the location of points of interests like banks and gas stations),

[1] http://healthland.time.com/2012/12/04/top-10-health-lists/slide/junk-no-more/.

the ENCODE catalog is now routinely used by researchers worldwide to zoom in on regions of interest in the human genome that are important for their studies. In fiscal year 2014, NHGRI will begin to add another layer of knowledge to this map with the launch of the Genomics of Gene Regulation (GGR) initiative. GGR will fund research to decipher how genes are regulated and to understand how gene regulation affects the function of cells and tissues, human development, and disease.

In fiscal year 2014, NHGRI also will continue advancing the discovery of the genomic bases of disease. For example, the search for genes that play a role in rare diseases will be accelerated through the work of NHGRI's Centers for Mendelian Genomics, as well as an extramural expansion of the highly successful NIH Undiagnosed Diseases Program. Through research programs such as the Large-Scale Genome Sequencing and Analysis Centers, the genomic underpinnings of common complex diseases, such as cancer, diabetes, autism, and Alzheimer's disease, will remain a focus within NHGRI's portfolio as well.

IMPLEMENTING GENOMIC MEDICINE

With the increasing accessibility of genomic technologies, the utility of genomics is already being demonstrated in clinical areas such as pharmacogenomics, non-invasive prenatal testing, infectious disease diagnostics, and cancer. The largest class of drugs now with FDA-required pharmacogenomic information to guide use on their labels includes those used for the treatment of cancer. Further, genome sequencing to identify mutations in a tumor's DNA sequence is now commonplace in the research setting and beginning to be seen in the clinical setting. Current examples of genomics informing care include the widespread use of "BRCA" testing in patients with familial risk factors for breast and ovarian cancer, the use of testing to predict breast cancer recurrence, and the use of genomic diagnostic tests to determine the suitability of particular treatments such as trastuzumab (Herceptin®) use in breast cancer, vemurafenib (Zelboraf®) use in melanoma, or crizotinib (Xalkori®) use in lung cancer.

In fiscal year 2014, NHGRI also will continue extending its portfolio to investigate the methods and evidence needed to integrate genomics as a standard component of clinical care. Both existing (e.g., CSER program) and new (e.g., Genomic Medicine Pilot Demonstration projects and the Genomic Sequencing and Newborn Screening Disorders program) initiatives will be carried out by integrated research teams that include clinicians, scientists, and bioethicists. These multi-disciplinary groups will examine the medical as well as the ethical, social, and legal issues involved with making genomic data an essential, broadly accessible and broadly desirable element to inform clinical care. In fiscal year 2014, the Institute will continue supporting research pertaining to the pursuit of genomic research and the realization of genomic medicine, including protecting research participant privacy, determining when to return individual results, and how to handle unanticipated, but clinically important, "incidental findings".

Through these and other programs, NHGRI will continue to lead the field of genomics in an effort to benefit the broad biomedical research enterprise and to realize the goal of advancing human health through genomics research.

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

Mr. Chairman and members of the committee: 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 (NIH). The fiscal year 2014 NIBIB budget request of $338,892,000 is $1,164,000 more than the comparable fiscal year 2012 level of $337,728,000. The mission of NIBIB is to improve human health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating the engineering and physical sciences with the life sciences to advance basic research and medical care. As we enter our second decade as an NIH Institute, NIBIB is continuing to build on that integration.

From wound healing to finding ways for the human body to create new cartilage for damaged joints, advances in regenerative medicine are helping wounded warriors and an aging population. Robotic leg prostheses with powered knee and ankle joints and other efforts in rehabilitation engineering hold the promise of giving once unimaginable independence to people who are severely paralyzed or have lost limbs. Advances in the field of nanotechnology, such as the ability to deliver drugs directly into tumors while sparing healthy tissue, and using imaging technologies for non-

invasive treatment as well as diagnostics, hold the potential to make healthcare more precise and more effective for patients.

ADVANCES IN REGENERATIVE MEDICINE

NIBIB is at the forefront of the developing field of tissue engineering and regenerative medicine, and already advances in stem cell research are being developed to aid our wounded warriors and the general population. Working toward this goal is the Armed Forces Institute for Regenerative Medicine (AFIRM), which includes NIBIB-funded researchers and more than thirty U.S. universities and companies. Research supported by AFIRM has developed advanced treatment options and accelerated delivery of regenerative medicine therapies to treat the most severely injured U.S. service members. An exciting example of just one of the many innovative projects under way is the development of bioprinting of skin for battlefield injuries. This technology uses a bioprinter that creates and delivers skin cells and biomaterials to rapidly cover large wounds, which are a major cause of morbidity and mortality in severe burn injuries in civilians and military personnel. Other efforts are focusing on the difficult repair of segments of bone and nerve that are lost or damaged following traumatic injuries.

In the general population, injury to cartilage can lead to joint pain and arthritis. One regenerative medicine project may help patients with knee injuries to successfully regenerate new, working cartilage through an innovative technique developed by NIBIB-funded researchers. The technique uses an engineered 'biogel' scaffold (a structure that supports and holds cells together) that solidifies when exposed to light, combined with a strong biological adhesive that covers the injured area and provides an environment that promotes the growth of cartilage-producing cells. This successful research led to a small clinical trial in patients undergoing microfracture surgery, a first-line therapy for cartilage repair where holes are drilled in the cartilage to encourage new growth. Patients who received the biogel and adhesive, in addition to microfracture surgery, had improved cartilage growth, less scarring, and decreased pain at 6 months post-surgery, when compared to microfracture without the biogel treatment. The technique has the potential to transform the field of knee cartilage repair, which affects many people and is difficult to treat successfully. A larger clinical trial using this promising technique is currently in progress. While the clinical trials are not funded by NIBIB, these are examples of public private partnerships of translating research to clinical settings.

REHABILITATION ENGINEERING TO ENABLE INDEPENDENCE

Overcoming major barriers, researchers have now developed an implantable, compact, self-contained device for the sensing and transmission of brain activity. The device is an important step toward the development and use of brain-computer interfaces that harness the power of thought to remotely control computers, prosthetics, and other devices. The new wireless device allows the user more freedom of movement than the earlier version, which was connected to a computer with wires and cables and greatly limited the range of movement. The small device is fully implanted beneath the skin much like a cochlear implant. It is capable of recording neural activity from 100 different sites and converting this neural activity into digital signals. It also transmits these digital signals to a wireless receiver located some distance outside the body. The device is recharged wirelessly. Initial tests in animals were successful at recording data in real-time for more than a year. The device may one day be used to control prosthetic arms and other devices, motorized wheelchairs, or for diagnostic monitoring in disorders such as in epilepsy, where patients currently are tethered to the bedside during assessment.

ENGINEERING ADVANCED MEDICAL SOLUTIONS

NIBIB continues to support technologies for more efficient and effective drug delivery. Key developments include the creation of nanoparticles that can target powerful cancer-killing medications to a tumor without inadvertently damaging surrounding healthy tissues. In addition to successfully targeting the tumor, a drug that is tethered to a nanoparticle can only reach its target if it survives in the blood, where the immune system is constantly removing foreign particles. To address this technical hurdle, researchers devised a stealth coating for nanoparticles that tricks the immune system into ignoring the particles. By disguising the nanoparticles to chemically look like "self", the immune system does not clear the particles, and more medication can be delivered to their target tumors. Using this method, tumors in mice were reduced by 70 percent compared with tumors that were targeted with the cancer drug but without the nanoparticle and stealth coating. Based on these encouraging results, human clinical trials using stealth-coated nanoparticles to deliver

anticancer drugs are currently under way. This technology might one day be used to deliver genes for gene-therapy treatment or to enhance biocompatibility and durability of larger foreign objects such as pacemakers and implants, whose function can degrade over time due to attacks by the immune system.

NIBIB also supports research that harnesses the power of magnetic resonance imaging (MRI) and the faster metabolic rates of cancer cells than normal cells to develop a biomarker for prostate cancer. The goal is to use the biomarker to distinguish which prostate cancer disease is aggressive from those that are indolent where watchful waiting may be the appropriate course of action. Researchers have developed a technique using hyperpolarized carbon-13 (C–13) compounds to measure the faster metabolism of glucose in prostate cancer. In this method, by "hyperpolarizing" the carbon isotope, investigators are able to increase the target signal by about 10,000-fold, making this carbon labeled signal much more readily detectable. The researchers developed a system for synthesizing, hyperpolarizing, and rapidly delivering carbon-13-labeled pyruvate, a product of glucose metabolism. The metabolic changes of pyruvate to lactate serve as a biomarker or indication for prostate cancer as the disease progresses and provide useful measures of the aggressiveness of the tumor. Preliminary clinical results show promise for this approach for cancer biomarkers.

NEW USES OF ULTRASOUND FOR DIAGNOSIS AND TREATMENT

The immune system's natural killer (NK) cells are those that find and destroy foreign substances in the body. A human NK cell line, NK–92 can be used to target and destroy tumors. However, this promising strategy to use the immune system to fight tumors is not possible for use in the brain because NK cells cannot penetrate the blood brain barrier (BBB). NIBIB-funded researchers developed an experimental system using ultrasound to deliver NK–92 cells to tumors in the brain. The movement of the NK cells into the tumor was monitored with and without focused ultrasound disruption of the BBB. Using MRI, researchers found that approximately 1 NK cell for every 100 tumor cells had reached the brain when using focused ultrasound to open the BBB, compared to 1 NK cell per 1,000 tumor cells when ultrasound was not used. These preclinical results suggest that the tumor-killing ability of immune natural killer cells combined with focused ultrasound has tremendous potential for targeting and destroying brain tumors.

Another new ultrasound imaging technique developed by NIBIB-supported researchers can noninvasively detect tumors and fibrosis in the liver. Typically, liver disease is diagnosed using liver biopsy, a surgical procedure that can be painful and cause complications. This new ultrasound-based technique, called Acoustic Radiation Force Impulse imaging does not produce harmful ionizing radiation and is relatively inexpensive compared with other imaging modalities. This means it can be used more frequently to track the progression of fibrosis. In contrast to a biopsy, which can only examine a small discrete sample of the liver, this method examines the entire liver. The technique uses focused, high intensity sound waves to produce "push-pulses" that generate shear within tissue. Ultrasound is then also used to monitor the tissue response. The tissue response is related to the stiffness properties and structure of the liver, and is displayed as a high resolution, qualitative image. This technique can also produce quantitative stiffness measurements based on the speed of the shear waves. These measurements are used to quantify specific levels of fibrosis that can be used to classify different stages of liver fibrosis or tumors.

Yet another advance is the use of the mechanical force of ultrasound to breakup thrombi and minimize the damage to heart muscle during a heart attack. Researchers first demonstrated in porcine models of coronary arteries blocked by blood clots or thrombosis, that conventional ultrasound using a high "mechanical index" in conjunction with micro-bubbles and a conventional clot dissolving agent achieved greater restoration of flow in the blocked artery. Consequently, there was also greater heart muscle salvaged. In an initial human study, this technique was successfully and safely used in patients who presented at a hospital with evidence that a heart attack had begun. If the promise of these preliminary studies continues, this could be implemented at hospitals throughout the country as a first-line treatment to minimize damage in evolving heart attacks.

NIBIB will continue to target the unique scientific opportunities of the 21st century in rehabilitation engineering, regenerative medicine, and advanced imaging techniques to improve disease diagnosis and treatment. This era promises a revolution in employing technology to realize innovations that address healthcare challenges, reduce disease mortality and morbidity, and enhance quality of life and improve the health of the Nation.

PREPARED STATEMENT OF CHRISTOPHER P. AUSTIN, M.D., DIRECTOR, NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

Mr. Chairman and members of the committee: 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 2014. The fiscal year 2014 budget for NCATS is $665,688,000, which represents an increase of $91,391,000 over the fiscal year 2012 comparable level of $574,297,000. The request includes $50 million for the Cures Acceleration Network (CAN), an increase of $40 million over fiscal year 2012. CAN will fund initiatives designed to address scientific and technical challenges that impede translational research, including support for the Tissue Chips for Drug Screening Initiative, the Discovering New Therapeutic Uses for Existing Molecules Program, and other programs. Common Fund support of these programs will end by fiscal year 2014, at which time they will be funded through the NCATS direct appropriation.

NCATS' mission is to catalyze innovations that enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. In the short time since its founding in December 2011, NCATS has become a hub of innovation for translational sciences at NIH and in the broader translational ecosystem that includes the pharmaceutical, biotechnology, venture capital, regulatory, and patient advocacy communities. The Center has launched several major research initiatives, cultivated promising strategic partnerships, and established a presence at NIH and in the community. For example, NCATS' Therapeutics for Rare and Neglected Diseases (TRND) program was responsible for the development and first-in-human testing of new therapies for four different diseases in a period of 16 months via novel partnership structures. Another achievement was the agreement with the Defense Advanced Research Project Agency and the Food and Drug Administration (FDA) to initiate an innovative grant program to create new tools for predicting drug toxicity. The goal is to fund researchers who will create 3–D "chips," which are miniature models with the structure and function of human organs. These chips will be used to test drugs to see if they are safe or toxic to humans, thus saving researchers time and money compared to current methods. NCATS also developed the New Therapeutics Uses for Existing Molecules initiative, a breakthrough partnership program with eight pharmaceutical companies to find new uses for existing drugs owned by these companies. The eight companies agreed to make many of their molecular compounds available to outside researchers for testing for new therapies. These compounds have already undergone safety and toxicity testing in humans and so provide researchers with valuable data that may help speed the research process forward. In addition, NCATS has created template agreements with the drug companies ready for use by the investigator, thus saving the time the investigator would have spent negotiating an agreement with the drug company.

Collaborations among Government, academia, industry and nonprofit patient organizations are crucial for successful translation. For example, support from the NCATS' Clinical and Translational Science Award (CTSA) program at the University of Pittsburgh contributed to the development of a robotic arm that allowed a quadriplegic patient to feed herself using just her thoughts. This remarkable achievement was the result of NIH, the Department of Defense, the Department of Veterans Affairs (VA), the FDA, a private foundation, two academic research centers, and a private company working together, which made this possible.

AVOIDING DUPLICATION, REDUNDANCY AND COMPETITION

A fundamental principle of NCATS is that it addresses the many translational problems that are not undertaken by industry because this early-stage research hasn't yet proven to be commercially viable. Thus, NCATS is explicitly complementary to efforts in industry. Our work is in the "precompetitive" space where industry and NIH/academia have long collaborated to mutual benefit.

In addition to this general positioning of NCATS as an "adaptor" or "intermediary" between academic and industry science, many specific initiatives have been put in place to prevent duplication, redundancy, and competition with industry. We recently published a Notice in the Federal Register that enumerates and seeks comments on the procedures and methods NCATS is using to ensure that industry is both aware of and able to provide input on our activities and planned initiatives. Some of these methods include frequent updates to the NCATS Web site, an NCATS Director's newsletter, publication of Requests for Information on proposed programs, open public meetings to which industry representatives are specifically invited, and meetings arranged with industry trade groups and associations.

PRE-CLINICAL RESEARCH: CONNECTING LABORATORY POTENTIAL WITH CLINICAL PROMISE

NCATS is active in the development, demonstration, and dissemination of a broad range of technologies, tools, and resources that facilitate collaborative pre-clinical testing and first-in-human clinical trial implementation. For example, NCATS' Matrix Screening "Platform," or testing process that includes specific equipment, is a transformative technology that identifies combinations of drugs to treat diseases resistant to single drugs, which is particularly important for treatment-resistant cancers. Since this testing is done in a high-speed fully automated robotic format, thousands of drug combinations can be tested in a single day to determine which are best able to kill the cancer cells while minimizing toxic side effects.

Determining toxicity is a major roadblock in the advancement of promising discoveries. The Tox21 Program, along with the Environmental Protection Agency, the National Institute for Environmental Health Sciences, and the FDA, is testing over 10,000 drugs and environmental chemicals for hundreds of activities relevant to toxicity, with all data being made publicly available.

CLINICAL RESEARCH: DEMONSTRATING MEDICAL BENEFIT

Clinical research is conducted to test the safety and effectiveness of a new or improved diagnostic or therapeutic intervention, more effectively diagnose a disease, demonstrate the utility of biomarkers or prognostic risk factors, and discover better ways to implement health-improving interventions. The centerpiece of this area at NCATS is the CTSA program.

The purpose of the CTSA program (http://www.ncats.nih.gov/research/cts/ctsa/ctsa.html) is to support the entire spectrum of translational research in order to accelerate the transition of laboratory discoveries into patient studies and into clinical practice. Through integrated homes that build on academic institutions' scientific strengths, CTSAs provide expertise, resources, and workforce training, which improve the quality, validity, generalizability, and efficiency of clinical and translational research. For example, a team of scientists with support from the University of California, Davis, CTSA developed a test to determine the prevalence of a debilitating disease, called Fragile X, in the general population. This information will help researchers create screening and diagnostic strategies and allow planning of clinical trial recruitment strategies for new Fragile X therapies.

FOCUS ON RARE DISEASES

Targeting support to accelerate new treatments for rare diseases is a major priority for NCATS. About 6,000 rare diseases affect an estimated 25 million Americans; and, according to the Office of Orphan Products Development, FDA, 450 orphan drugs have been approved, which together treat only 250 of the 6,000 diseases. Discoveries about the molecular basis of rare diseases based on the Human Genome Project offer unprecedented scientific opportunities to change systematically this landscape, by approaching rare diseases and their treatment as a holistic systems-based problem, and NCATS is capitalizing upon these opportunities. For example, the TRND program speeds the development of new treatments for rare diseases of very low prevalence and otherwise commercially neglected tropical diseases. It forms public-private partnerships, which leverage the unique strengths and capabilities of each party. Partnerships with disease foundations and/or biotech firms helped bring promising therapies to the first-in-human testing stage for chronic lymphocytic leukemia, sickle cell disease, hereditary inclusion body myopathy, and Niemann-Pick Type C disease.

CONCLUSION

NCATS has sought to establish new technologies and paradigms that can be implemented broadly to improve the efficiency of the translational process for all and to broker collaborative development of new interventions. We are grateful for the support of this subcommittee for this new Center and look forward to sharing progress with you each year.

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

Mr. Chairman and members of the committee: 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 2014 FIC budget of $72,864,000 includes

an increase of $3,371,000 over the comparable fiscal year 2012 appropriation of $69,493,000.

From leading the call for an AIDS-free generation to developing vaccines and therapeutics for diseases that affect populations worldwide, the United States is a global leader in health research and scientific advances that improve the lives of Americans and people across the globe. These discoveries are often made by U.S. and foreign scientists working in close collaborations that enable the best and brightest minds to tackle complex health challenges together. The Fogarty International Center therefore supports innovative training and research programs for U.S. and low- and middle-income country (LMIC) scientists that strengthen the research capabilities and catalyze the international scientific partnerships that lead to research discovery and improved health. By investing in current and future leaders in global health research and strengthening the long-term capacity of research institutions to provide robust and sustainable platforms for cutting-edge science, Fogarty advances the goals and extends the leadership of the NIH and the U.S. Government in science and research, while playing a vital role in building the capacity needed to successfully tackle critical health challenges.

RECRUITING AND RETAINING DIVERSE SCIENTIFIC TALENT AND CREATIVITY

Fogarty programs have supported long-term research training for more than 4,500 scientists worldwide, in collaboration with more than 230 U.S. and LMIC research institutions. These investments provide unique training opportunities for early-career global health researchers, and aid in the retention of diverse scientific talent in the research enterprise. The vast contribution of FIC programs can be seen in the over 5,000 PubMed publications citing FIC awards over the last 5 years alone. Today's complex public health challenges benefit when investigators from diverse fields work together to produce transformative advances in science and technology. Fogarty's unique "Framework Program for Global Health Innovation" trains multidisciplinary teams of postdoctoral researchers to work together to produce fresh insights into global health problems and develop effective innovations for implementation in low-resource settings. For example, with Fogarty support, a team of medical, engineering, and architecture researchers from Boston, South Africa, and Peru is designing and validating effective, affordable prototypes for air disinfection. This work can not only help prevent airborne infections such as tuberculosis and influenza from spreading in the low-resource settings where they cause significant illness and death, but can also potentially help higher income countries such as the United States improve their programmatic approaches to airborne infection.

—Funded under the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) in collaboration with 18 NIH Institutes and Centers, Fogarty and the Health Resources and Services Administration (HRSA) jointly co-administer an innovative cross-U.S. Government initiative funded primarily by the Office of the Global AIDS Coordinator (OGAC) that is transforming medical education and research training for medical students in 12 African countries. The 13 direct MEPI awardees and more than 40 partner institutions use a broad range of state-of-the-art teaching and collaboration tools to train the next generation of scientific leaders to solve their country's most pressing health problems—from HIV/AIDS to maternal and child health, and non-communicable conditions such as mental health and cardiovascular disease. MEPI is increasing the quality, quantity, and retention of medical faculty and physicians with research skills, and building relationships with the public sector partners that promote sustainable research capacity. For example, Zimbabwe's Ministry of Education is now co-funding the University of Zimbabwe's MEPI work.

TRANSLATIONAL SCIENCE

Fogarty programs support researchers who are generating the critical scientific evidence that can be applied to specific interventions, policies, and programs, and make a difference in fighting disease and improving health.

—In recent years, we have seen that infectious diseases from animal as well as human hosts can cause outbreaks that pose significant health and economic threats to the U.S. and other countries, Fogarty's "Research and Policy in Infectious Disease Dynamics (RAPIDD)" program—co-funded by the Department of Homeland Security (DHS)—brings together senior infectious disease modelers and postdoctoral fellows to conduct the research and develop infectious disease modeling approaches that can help the U.S. and other policymakers plan for and respond to potential infectious disease threats. "RAPIDD" models have contributed to a greater understanding of how Avian Influenza and Hand, Foot,

and Mouth disease can develop into outbreaks from an initial case, and how these outbreaks can be controlled effectively.

TODAY'S BASIC SCIENCE FOR TOMORROW'S BREAKTHROUGHS

Fogarty supports catalytic basic biomedical and behavioral research that can lead to tomorrow's breakthroughs.

—Despite recognition of a looming antibiotic resistance crisis in the U.S. and around the world, the number of new antibiotics reaching the clinic continues to decline sharply, and most recent discovery has been confined to minor modifications of known antibiotics, with limited new therapeutic potential. The Fogarty International Cooperative Biodiversity Groups (ICBG) program, is working to change this. Fogarty-funded researchers have developed an innovative and cost-effective approach to antibiotic discovery, using an "antibiotic mode of action profile" (BioMAP). BioMAP is a ground-breaking tool that can be used to facilitate new natural products antibiotic discovery and address the looming antibiotic crisis in the United States and around the world.

—Brain disorders such as epilepsy and Alzheimer's pose significant health problems around the globe. Fogarty's "Brain Disorders" program supports cutting-edge basic science research in LMICs on the nervous system—research that could lead to new diagnostics, prevention, and treatment strategies. In India, for example, Fogarty grantees are exploring why Alzheimer's affects Indian populations less than populations in developed countries, with the goal of discovering useful evidence to understand and mitigate Alzheimer's globally. In Uganda, Fogarty-supported research is creating a base of knowledge on dementia in those with long-term HIV infection, obtaining data on prevalence, risk factors, and possible differentiation by HIV sub-type that will be useful in understanding the course of the disease and developing potential interventions worldwide.

FUTURE CHALLENGES

The need for sustainability poses a significant challenge for investments in global health research and research training. Fogarty investments continue to evolve with increasing research capabilities in LMICs in order to build on successes and support the training of individual scientists and strengthen research institutions. Fogarty's deep regional expertise will continue to serve as a unique resource for NIH and individual foreign scientists, institutions and countries that are seeking new models and mechanisms that enable collaboration around areas of mutual interest. In addition, Fogarty will increase support for institutional networks and hubs for data collection and sharing. When such sharing platforms are built around a core of trained individuals and strengthened institutions, they can harness effectively the different strengths of these institutions, and promote enhanced efficiencies and more robust, collaborative science.

—Fogarty envisions that its U.S.-LMIC "GEOHealth" hubs will become global leaders in the collection, management, synthesis, and interpretation of data on environmental and occupational health, serving the larger multi-national regions in which they reside as well as supporting research of great relevance to both these LMIC regions and the U.S.

—In sub-Saharan Africa, universities supported by "MEPI" are emerging as regional training centers and upgrading the technology to enable distance learning and resource-sharing among institutions. This model is revolutionizing African medical education and research training by enabling partner institutions across Africa to pool their areas of expertise, share teaching tools, and ensure that all students receive the highest-quality instruction from the continent's best qualified faculty and researchers.

In an increasingly interconnected world, the U.S. is often called upon to play a leading role in addressing the world's most pressing challenges. Fogarty programs harness the capabilities of the U.S. as a leader of biomedical research, extend the frontiers of science, accelerate discovery, improve the health of Americans and people across the globe, and help the U.S. continue to compete and lead in science.

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

Mr. Chairman and members of the committee: 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 2014 budget of $382,252,000 includes an

increase of $17,365,000 over the comparable fiscal year 2012 level of $364,887,000. 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. 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 development in electronic health records, clinical decision support, natural language processing, information retrieval, imaging, computational biology, telecommunications, and disaster response.

NLM's programs and services directly support NIH's key initiatives in basic research, translational science, and research training, as well as in Big Data. 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. NLM's PubMed Central (PMC) provides essential infrastructure for the NIH Public Access Policy, which since 2008 has made published NIH-funded research freely and permanently available to the public.

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. NLM is a primary source for results of patient-centered outcomes research, providing access to evidence on best practices to improve patient safety and healthcare quality. The Library maintains an expanding collection of full-text guidelines, evidence summaries, and systematic reviews from authoritative agencies and organizations around the world.

NLM is also a hub for the international exchange and use of data utilized in molecular biology, genomics, and clinical and translational research. Many NCBI databases, including dbGaP, the Genetic Testing Registry (GTR) and ClinVar, are fundamental to the identification of important associations between genes and disease, and to the translation of new knowledge into better diagnoses and treatments. NLM's Lister Hill National Center for Biomedical Communications operates ClinicalTrials.gov, the world's most comprehensive clinical trials database. It contains registration data for more than 145,000 clinical studies with sites in 185 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 (FDA) Amendments Act of 2007. Summary results are available for nearly 9,000 completed trials of FDA-approved drugs, biological products, and devices—providing a new and growing source of evidence on efficacy and comparative effectiveness. NLM will leverage experience with these resources and its research in related fields to contribute to NIH efforts to improve access to other types of NIH-funded Big Data.

HEALTH DATA STANDARDS AND ELECTRONIC HEALTH RECORDS

Electronic health records (EHRs) with advanced decision-support capabilities and connections to relevant health information are essential to improving healthcare 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 prod-

ucts and personal health record tools. As the Department of Health and Human Services (HHS) coordinating body for clinical terminology standards, NLM works closely with the Office of the National Coordinator for Health Information Technology and the Centers for Medicare and Medicaid Services to facilitate adoption and "meaningful use" of EHRs. NLM supports, develops, and distributes key terminology standards now required for U.S. health information exchange. To help EHR developers implement standard terminologies, NLM produces related software tools, frequently used subsets, and mappings to administrative code sets, and provides the authoritative versions of terminology value sets for required clinical quality measures. NLM's MedlinePlus Connect also supports meaningful use by providing a way for EHR products to link patients to high quality health information relevant to a specific health conditions, medications, and tests, directly from their EHRs.

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 Department of Health and Human Services (DHHS) 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 Database. 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 6,000-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.

INFORMATION FOR DISASTER AND EMERGENCY RESPONSE

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 and ensuring continued access to health information in emergencies, including 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. Mobile apps and tools developed for first responders have been downloaded nearly 500,000 times worldwide.

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 JACK E. WHITESCARVER, PH.D., DIRECTOR, OFFICE OF AIDS RESEARCH

Mr. Chairman and members of the committee: I am pleased to present the President's budget request for fiscal year 2014 for the trans-NIH AIDS research program, which is $3,121,716,000. This amount is $46,921,000 above the comparable fiscal year 2012 level of $3,074,795,000. It includes the total NIH funding for research on HIV/AIDS and the wide spectrum of AIDS-associated malignancies, opportunistic in-

fections, co-infections, and clinical complications; intramural and extramural research; research management support; research centers; and training.

NATIONAL INSTITUTES OF HEALTH AIDS RESEARCH ACCOMPLISHMENTS

In the three decades since AIDS was first reported, NIH has been the global leader in research to understand, prevent, diagnose, and treat HIV and its many related conditions. From the development of the first blood test for HIV infection and the discovery and clinical testing of the first effective therapies, through today's research to determine whether a vaccine, microbicide, or eventual cure for AIDS will one day be possible, NIH research has transformed HIV 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 since 1995 by the use of AIDS therapies developed as a result of NIH-funded research. Recent discoveries include:

—Development of new treatments for many HIV-associated co-infections, comorbidities, malignancies, and clinical manifestations;
—Development of new strategies for the prevention of mother-to-child transmission (MTCT), which have resulted in dramatic decreases in perinatal HIV in the U.S., where now fewer than 100 babies a year are born with HIV infection;
—Demonstration of the first proof of concept that a vaccine can prevent HIV infection and identification of potential immune markers for protection;
—Discovery of more than 20 potent human antibodies that can stop up to 95 percent of known global HIV strains from infecting human cells in the laboratory;
—Demonstration of the first proof of concept that a microbicide gel can prevent HIV transmission;
—Demonstration that the use of antiretroviral therapy by infected individuals can reduce HIV transmission to an uninfected partner dramatically;
—Demonstration of the feasibility of pre-exposure prophylaxis (PrEP), the use of antiretroviral treatment regimens by uninfected individuals to reduce their risk of HIV acquisition;
—Discovery that genetic variants may play a role in enabling some individuals, known as "elite controllers," to control HIV infection without therapy;
—Critical basic science discoveries that continue to provide the foundation for novel research; and
—Advances in basic and treatment research aimed at eliminating viral reservoirs in the body that for the first time are leading scientists to design and conduct research aimed at a cure for HIV/AIDS.

THE AIDS PANDEMIC

In spite of these advances, the HIV/AIDS pandemic remains a global scourge. UNAIDS reports that in 2011, more than 34 million people were estimated to be living with HIV/AIDS; 2.5 million were newly infected; and 1.7 million people died of AIDS-related illnesses. The majority of cases worldwide are the result of heterosexual transmission, and women represent more than 50 percent of HIV infections worldwide. More than 25 million men, women, and children worldwide have already died. Around 330,000 children were newly infected with HIV in 2011, a reduction of 24 percent in just 2 years—from 2009–2011—a result of the distribution of HIV treatment to prevent mother-to-child transmission developed by NIH research.

In the United States, the Centers for Disease Control and Prevention estimates that approximately 1.2 million people are HIV-infected; approximately 50,300 new infections occur each year; and one in four people living with HIV infection in the U.S. is female. HIV/AIDS continues to be an unrelenting public health crisis, disproportionately affecting 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 over the age of 50.

COORDINATED TRANS-NIH AIDS RESEARCH PROGRAM

The NIH AIDS research program is coordinated and managed by the Office of AIDS Research (OAR), which functions as an "institute without walls" with responsibility for AIDS-related research supported by nearly every NIH Institute and Center (IC). OAR coordinates the scientific, budgetary, and policy elements of the trans-NIH AIDS research.

Through its unique trans-NIH planning, budget, and portfolio review processes, OAR identifies the highest priority areas of scientific opportunity and ensures that precious research dollars are invested effectively.

In collaboration with both Government and non-Government experts, OAR develops the trans-NIH AIDS strategic Plan. The priorities of the Plan guide the development of the trans-NIH AIDS research budget. OAR develops each IC's AIDS research allocation based on the Plan, scientific opportunities, and the IC's capacity to absorb and expend resources for the most meritorious science—not on a formula. This process reduces redundancy, promotes harmonization, and ensures cross-Institute collaboration. OAR has the authority to shift resources across ICs and areas of science to meet the needs of the changing epidemic and scientific opportunities.

NEW SCIENTIFIC ADVANCES AND OPPORTUNITIES

The 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 U.S. and around the world. These advances represent the building blocks for the development of this trans-NIH AIDS research budget request. These include:

—Basic research that will underpin further development of critically needed "vaccines and microbicides".

—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".

—Critical studies in the area of "therapeutics as a method to prevent infection", including treatment to prevent HIV transmission; Pre-Exposure Prophylaxis; 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.

—Research to develop better, less toxic treatments and to investigate 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 to address the increased incidence of malignancies; cardiovascular, neurological and metabolic complications; and premature aging associated with long-term HIV disease and antiretroviral treatment (ART).

—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.

FUNDING PRIORITIES

OAR has utilized its authorities to shift AIDS research resources across ICs to meet the new and exciting scientific opportunities in AIDS research. These shifts reflect the scientific priorities identified in the annual trans-NIH strategic planning and budget process and address the evolving clinical profile of the epidemic, changing demographics, and most recent scientific advances. In this budget request, OAR has provided increases to high-priority basic research (etiology and pathogenesis) that provides the underlying foundation for all HIV research. An important area will focus on research related to the potential for a cure or lifelong remission of HIV infection, including studies on viral persistence, latency, and reactivation. Increases are also provided for the development of vaccines and microbicides to prevent HIV infection. In order to provide those increases, OAR has reduced and redirected funds from natural history and epidemiology, therapeutic clinical trials, and training and infrastructure support.

SUMMARY

The NIH investment in AIDS research has produced groundbreaking scientific advances. AIDS research also is helping to unravel the mysteries surrounding many other cardiovascular, malignant, neurologic, autoimmune, metabolic, and infectious diseases, as well as the complex issues of aging and dementia. 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, again, Dr. Collins, for your statement, and for bringing us up-to-date.

We'll begin a round of 5-minute questions.

Who is running the time here? There we go.

So we'll begin a round of 5-minute questions. I'm sure we'll have more than one round.

FAVORING SAFER VERSUS INNOVATIVE RESEARCH PROJECT GRANTS

So, Dr. Collins, as I said in my opening statement, I think you repeated it, that the reviewed NIH grants will drop to about 16 percent this fiscal year. I'm concerned that when money gets that tight, there's a tendency to shy away from awarding ideas that are thinking outside the box, and we've talked about that many times here with you over the last many years.

I'm concerned that, consciously or unconsciously, your peer reviewers might tend to favor safer incremental advances and to avoid ideas that are bolder but may carry more risk. Any validity to that?

Dr. COLLINS. Mr. Chairman, that's certainly an area of considerable concern for all of us, because imagine yourself on a study section where you have a big pile of exciting science in front of you and you know you're going to only be able to fund a very small number of those. You have in front of you a really powerful strong proposal that builds on previous work from an established investigator that you know is going to be successful, and then you got something over here that's a bit risky from an investigator who doesn't have the same track record.

If it works, it could be groundbreaking, but you're not sure it's going to work. And in that setting where you would love to fund both, but you may not be able to, there can be a tendency then to go with what you know is going to produce results. But that could be just the wrong thing to do.

We in NIH have a number of programs that aim to try to encourage innovation in this climate by setting up programs like the Pioneer Awards, the Transformative RO1s, the New Innovator awards. You can't apply to those programs unless you have an out-of-the-box idea.

So, there's this common fund effort to do that, and many of the institutes have initiated efforts of that sort as well.

But there's no question about it. There's no magic here in terms of loss of innovation potential. Just the fact that we're only funding 15, 16 percent or less of the applications that come in, there's a lot of innovation at the 18th percentile and the 22nd percentile. Most of us have a very hard time telling the difference between a grant that scores at the 11th percentile and the 17th. Yet, one is going to get funded and one may not.

So, the real anxiety we all feel is how much talent is being wasted and how many ideas are not getting followed up on that could be.

EFFECTS OF SEQUESTRATION ON RESEARCH PROJECT GRANTS

Senator HARKIN. So sequestration has an effect on that also?

Dr. COLLINS. Absolutely, because sequestration drops the—as we've all just mentioned, 700 grants that we hoped we would fund

this year are not going to be. I'm sure in those 700 there were some great, innovative, out-of-the-box ideas.

NCI'S PROVOCATIVE QUESTION INITIATIVE

Senator HARKIN. Okay. I'm going to go to Dr. Varmus, talking about thinking out-of-the-box and everything. Tell us more about your Provocative Questions program, and what's the purpose, and how is it proceeding?

Dr. VARMUS. We did two things to try to ensure that we do the best we can, imperfect though that is, to address the concerns you and many others have raised about risk-taking under these adverse fiscal circumstances.

The first thing we do is to look at a large number of our grant applications, and award grants even when the score is a little less than you might think is required for success by saying this is really innovative and addresses a very important issue.

Number two, we set up some special programs, one of which is called Provocative Questions. These questions come from groups that we assemble around the country, interdisciplinary groups, people who haven't been in cancer research before, to raise some difficult questions that we think technology now may be prepared to address. We have these questions debated on our Web site. We then invite applications for answering about 24 each year, and we're funding—last year, over 50; this year we hope more than that—to try to address the 24 questions that we've been selecting as particularly important and difficult questions.

Too early to say how well we're going to do with this, but it's a way to try to guarantee some answer to the question you're appropriately raising.

BRAIN INITIATIVE: WHAT IS IT?

Senator HARKIN. I'll have a follow-up question on that later, but I wanted to ask Dr. Landis, in the short time I have left, about the new BRAIN Initiative.

The President talked about mapping the brain, what does it mean? Someone compared it to, again, the Human Genome Project. But even at the beginning, some of us were there at the beginning, we knew what the end result was going to be, and we knew when it was going to end. We didn't know exactly when, but we knew what the end result was.

What do we know about what is the end result? Is there something that we're looking to reach at a certain point in time?

Dr. LANDIS. So, what we would really like to be able to do with the BRAIN Initiative is to understand how information is processed in circuits. As Dr. Collins told you, we're beginning to have better maps of connections between nerve cells in different regions of the brain. And, we can lay them out in circuits that control particular movements, vision, or hearing.

But what we don't understand is how information is processed through those pathways. And in order to understand a number of psychiatric diseases and even neurodegenerative diseases, we have to understand how circuits work. We simply do not have the tools to do that now. So, that would be one of the major goals for the first 5 years of the BRAIN Initiative, to get better tools and tech-

nologies that will be able to help us track activity in circuits, and understand how information changes as it goes from one nerve cell in a circuit to another.

Much more, as I've already said to Dr. Collins, much more complicated than just lining up the As and Cs and Ts and Gs, but could have as much, or even greater, impact. And he did agree with me on that.

Senator HARKIN. Yes, but 3 billion base pairs, we thought that was a lot. Now we're talking about a trillion or something like that. I don't know. We'll get back to that.

Senator Moran.

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

Dr. Collins, thank you very much for your compelling testimony.

Dr. Varmus, thank you for coming to Kansas City and visiting a couple of facilities, a research facility and a hospital. But thank you especially for riding your bike to raise money for cancer research.

Dr. VARMUS. Along with the barbeque.

Senator MORAN. Along with the barbeque. That's right. That was the real inducement. Thank you very much for highlighting Kansas City barbeque.

BRAIN INITIATIVE: 10-YEAR BUDGET

Dr. Collins, and this may be this is for Dr. Landis, because it's a follow-up to what the chairman was asking about. On the BRAIN Initiative, the budget documents are not very specific in regard to what we should expect as far as budget requests in the next 10 years.

I was interested in what the goals are in the short term of this project. You outlined already what, at least in the first 5 years, is the significant goal. But what would we as a committee, what would we as members of the Senate, expect the request to be in regard to the budget into the future?

Dr. COLLINS. So, a very appropriate question. This is sort of like the genome project in 1988 where it was clear there was an opportunity, and it wouldn't happen without a coordinated effort, particularly the focus on technology. But nobody was quite sure at that point what the trajectory could look like as far as accomplishing that goal.

We're in the process right now of trying to define that, Senator, in the long term, over the next 10 or 15 years. What could be accomplished? What would the steps be? What kind of technologies do we need? And what would the cost be?

So, we brought together a really remarkable group of visionary neuroscientists in a group—co-chaired by Cori Bargmann from Rockefeller and Bill Newsome from Stanford along with 13 other remarkable folks—and we've asked them, in the course of the next few months, and they're hard at work at this, to lay out some initial milestones of what this project needs to accomplish. And by the summer of 2014, to have a much more detailed roadmap of where the BRAIN Initiative needs to go and how quickly it can get there.

So, frankly, I don't have a clear answer to your question at the moment, in terms of what the budget trajectory of this might be

over the next 10 or 15 years. We have to be sure we have the science plan laid out.

Senator MORAN. And there's no justifiable reason that we should expect that plan at this point? That's just not accomplishable, at this point? Before we start down this path, we're not going to know what to expect?

Dr. COLLINS. I think at this point, it would be premature to try to attach budget numbers to a scientific plan that hasn't quite formed in a coalesced way and been embraced and endorsed by all of the scientific experts that we want to participate and to take part in this.

So, it has always been our view that if you're going to try to start something really bold, the first step is to map out the science, and then you figure out, okay, what does that mean in terms of the timetables and the costs? Of course, you have to set priorities within the realistic envelope of what costs might be available to you.

We recognize this may be a tough time to be starting a very ambitious project, but we just don't think it would be right to wait, given the opportunity.

STATUS OF NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

Senator MORAN. Dr. Collins, this might be for you, as I don't think the National Center for Advancing Translational Sciences (NCATS) director is here.

Dr. COLLINS. He is not.

Senator MORAN. Let me ask about the status of NCATS. I was supportive of its establishment. I think that is now about a year and a half ago. And I'd be interested in having you bring me up-to-date on its developments.

One of the environments in which NCATS now works is that with the economic conditions we face, private drug companies can no longer make a financially sound business case to invest in new drug development projects. There's this gap, what has been described as a valley of death between scientific discovery on the one side and patient benefit and commercial success on the other.

The goal of NCATS has been to fill that valley. What kind of success is NCATS having in doing that?

Dr. COLLINS. Well, thank you for the question.

Let me say right upfront how wonderful it's been for Chris Austin, the Director of NCATS, to work with folks in Kansas at the university and with the Leukemia and Lymphoma Society on a few groundbreaking projects. Particularly one on chronic lymphocytic leukemia (CLL), which is actually a good example of one of the things I want to mention that NCATS is catalyzed, and that is this whole idea of repurposing drugs that were developed for something but turned out to have a use for something else.

The project they're working on with Kansas is a drug developed for rheumatoid arthritis, Auranofin, which turns out to have activity against leukemia, and more recently to the delight of all of us, also against a very resistant kind of cancer called mantle cell lymphoma.

The CLL protocol is already well along in a clinical trial. This is an amazing quick turnaround, because if you had to start from

scratch, it would take years and tens of millions of dollars to get to a clinical trial. But, if you can identify a compound and try it for a new purpose, you already have all that background data and you shave off years and many, many tens of millions of dollars in cost.

So, NCATS is in fact catalyzing that kind of repurposing both for drugs that have already been approved but also in working with companies, eight of them, they have agreed to make 58 compounds available for new uses that actually turned out not to be effective for the original use but the drugs are known to be safe.

This is crowdsourcing, if you will, the opportunity to find a new use for a really heavily invested compound that may turn out to have failed for disease A but might be just the thing for disease B.

NCATS is also working with the Food and Drug Administration (FDA) and with Defense Advanced Research Projects Agency (DARPA) on developing a new and very high-tech way of identifying whether or not a drug is going to be safe before you ever give it to that first human patient, using a biochip depending upon the stem cell, iPS cell technology.

NCATS also serves now as the home for the largest investment in clinical and translational science, namely our Clinical and Translational Science Award (CTSA), of which they are 60 across the country in many of your States, and basically then bringing that network together in a way that makes the whole really much greater than the sum of the parts, sort of CTSA 2.0, as we are starting to call it.

So, I think even though NCATS has only been around for, you know, a year and maybe 5 months, the evidence is very clear that this is an opportunity that we have grabbed on to. The private sector is enthusiastic about the way in which this serves as a complementary set of contributions to what they are doing. Academics are fired up about it. I think this has turned out to be a really good thing for NIH, too.

Senator MORAN. Very good.

I assume you're the one who coined the phrase "valley of death" and now "crowdsourcing." I will use it in my comments next.

Dr. COLLINS. I don't think I can take credit, but you are welcome to use the terms.

Senator HARKIN. Senator Mikulski, Senator Shelby, Senator Cochran.

Senator Mikulski.

Chairwoman MIKULSKI. Thank you very much, Mr. Chairman.

And, Dr. Collins, I want to welcome you and your entire team, and also other heads of institutes who are not at the blue table but are certainly always at the head of the line at the head table.

I just wanted to just tell you in the warmest way, and to my colleagues, what a sense of joy and pride that I have representing NIH. The fact that it is located in my home State of Maryland, Senator Cardin and I both know that every day, to have such a premier institution is one of the reasons we want to be in the Senate, really to be an advocate for the kinds of resources, policy, and framework, so you get to be you and you get to be what the American people want you to do, which is to find cures to disease, to find

containments of disease, to look for those things to even prevent them from happening or prevent them from escalating.

So it's not only a source of pride, but I can tell you, as the chair of this full committee, I'm going to work with Senator Harkin and Senator Moran across party lines, to make sure they get the kind of allocation they need to do their job.

Much has been said here about sequester. I'm not going to go into it in detail, but I'm concerned about the negative impact that it has, first of all on the people who work at NIH and those who participate in the extramural programs, like the University of Maryland, like Hopkins, like the great land-grant universities that, again, are out there working every day. That's the genius of what we do.

It's not Government-owned and operated. It's also out there extramurally and also functioning around the world, because who you are, you talk to the others around the world.

And, therefore, we need to look at the impact of sequester on jobs, on the economy, and not only on our reducing public debt today, but the impact on growth.

I am just struck by what you've done. Deaths from heart attacks and strokes have fallen more than 60 percent—60 percent. A wonderful colleague like Mark Kirk could make it up the steps of the Capitol when he was sworn in for his comeback into the United States Senate because of his grit, his verve, and the medical science behind him.

This is not only for a member of the United States Senate; it's for all Americans.

HIV/AIDS—we remember, Dr. Fauci, when the crisis came. We were here when a little boy named Ryan White testified. He was kept isolated in his own class in school because nobody would talk to him. HIV/AIDS, thanks to your work and the brilliant scientists, are no longer a death sentence.

And for the children of the world in our own country, children with the most common childhood leukemia have a 90 percent chance of surviving.

What a phenomenal story.

Dr. Varmus, you were the Director of NIH. You go to Sloan-Kettering. You have one of those cushy, full professorships that most people dream about. You come back to head up an institute. You announce that cancer rates are down 12 to 15 percent across the board.

This is just stunning. And yesterday we saw a brilliant actress, an esteemed actress take the bold step, announcing the bold step where she had a prophylactic mastectomy in order to ensure her own survival rate. But she knew her genetic situation. She could have decisions, informed consent. This is who we are, and this is what we're fighting for.

I didn't mean to give a speech, but I'm so excited about you.

And I want to say to my colleagues, this is why we have to not only—this sequester I think has a very deleterious, eroding, and corrosive effect. So I want to do all I can to cancel sequester this year, and also cancel sequester for the next 9 years, for which you would then fall behind to the tune of $19 billion.

We hope that the other side—we've got support here on the other side of the aisle. I worry about the other side of the dome.

Mr. Ryan, in his budget, is sending it to us to work with at $966 billion. That's bad enough, but he took all of it out of domestic discretionary spending.

I'm not going to turn this into politics. We want to be above politics. But we're going to have to deal with politics.

I want my subcommittee chairman and the vice chairman of this subcommittee to know, I want to work with them, because what I see my job as doing is to do all we can to help you be you and help you do the mission that the United States of America and its people gave you.

So I'm going to work my earrings off to make that happen. And with that, I just wish we could even get more done.

I'm not going to ask questions. I've taken a lot of the time here. I will be interested in the further discussion that we're having.

Senator HARKIN. Madam Chairman, thank you very, very much for your leadership of this full committee, and not only your leadership of the full committee, but your great leadership on this particular subcommittee. For all of the input and leadership you've given us through all these years, we thank you very much.

Now, we'll turn to Senator Shelby.

Senator SHELBY. Thank you.

First of all, I want to associate myself with the remarks of Senator Mikulski. She said it so well.

I believe that the top investment we can make in America to save lives, to improve lives, for the American people is to invest in the NIH. I believe this.

I'd like to see us double NIH's funding. I know that's hard to do, but to at least get on the upward funding trend, not the downward trend, of biomedical research in this country is a critical first step.

And I'm saying that because I see the results of NIH research, as Senator Mikulski has pointed out, Senator Harkin has, and others, Senator Moran.

RESEARCH AND ITS IMPACT ON THE STANDARD OF CARE

Having said that, Dr. Collins, I want to get a little parochial, if I can.

Researchers at the University of Alabama in Birmingham, as you well know, conducted an important study on very premature babies, a study called "SUPPORT" from 2004 to 2009 that was funded by the National Institutes of Health. Researchers at more than 20 sites were trying to determine, as I understand it, the proper oxygen levels for these vulnerable premature babies by comparing two ranges of oxygen saturation within the standard of care at that time.

It's my understanding that the SUPPORT study has had an important effect on clinical care. Dr. Collins, how important is research like this that study and ultimately improve the standard of care?

Dr. COLLINS. Senator Shelby, thank you for the question.

Very important, indeed. Standard of care reflects what we know at the time, and oftentimes, we don't know enough, and so it may be a rather broad range of options and physicians and other care-

givers who are trying to do the best job of taking care of patients. And patients who are seeking the best care may not be well-served by all, the entire range, of opportunities that are called standard of care.

That was certainly the case for the study of the optimum oxygen levels to give to premature babies.

Senator SHELBY. But you learn by investigating and by studying. That's the bottom-line.

Dr. COLLINS. You're exactly right.

So, for us at NIH, we invest heavily in these kinds of studies. Let me give you another couple of examples.

Individuals who are going through hemodialysis, and there are a lot, sad to say, many of them because of diabetes. There has never really been a clear understanding of what the right schedule is for hemodialysis, how many times a week, how many hours. That's a huge impact on somebody's quality of life, in terms of how much time they're spending there. But also, quality of life is dependent on how effective the dialysis is. So, a study called the Frequent Hemodialysis Network (FHN): Daily Trial, that we have been funding, aimed to try to get an answer to that. All in the standard of care, everybody in that study, is getting the kind of treatment that you would consider standard, but we're trying to find the sweet spot, to do a refinement of that.

I could cite you two or three others. This is very important and yet we depend upon patient——

Senator SHELBY. It goes to the basis of your research, does it not?

Dr. COLLINS. Yes, it does. That's what our goal is, is to try to be sure that people get the best possible information in order to guide their medical care.

UNIVERSITY OF ALABAMA AT BIRMINGHAM INFANCY CLINICAL STUDY

Senator SHELBY. As you well know, the University of Alabama at Birmingham (UAB) received a letter from the Office of Human Research Protection (OHRP) about the SUPPORT clinical trial that we're carrying out under the auspices of NIH. And the OHRP determined that UAB should have informed parents of an increased risk of death of their infant by participating in the study. But it was my understanding that the risks were unknown at the time of the study's commencement in 2004, and there was no specific scientific data that existed at the start of the study that showed an increased risk.

Were babies in that study at any greater risk than babies not in the study? Do you know?

Dr. COLLINS. No, Senator. I don't believe they were.

Senator SHELBY. Okay.

INSTITUTIONAL DEVELOPMENT AWARDS PROGRAM ELIGIBILITY CRITERIA

We've talked about the sequester, I'll move on, on that. I'm committed to working with Senator Mikulski to see if we can plus-up NIH, though.

Institutional Development Awards (IDeA), we discussed this topic a little bit before. I think it's important to recognize that the next scientific discovery may come from anywhere. You don't really

know where. And I believe that institutions that do not historically have high NIH grant rates can still substantially contribute to biomedical research. And I believe we need to give these institutions an opportunity.

As we discussed before, Dr. Collins, the eligibility criteria for the IDeA program is outdated. Both the fiscal years 2012 and 2013 Senate Labor-HHS bills included report language regarding this issue.

However, it's my understanding that no significant information on the subject has ever been provided to the subcommittee.

Dr. Collins, could you work with us to develop a better criteria, eligibility criteria, for some of these institutions that really could contribute, if given a chance?

Dr. COLLINS. So, Senator, I know time is short, but I'll answer quickly. I do agree that it's a wonderful opportunity for capacity-building in this competitive program that is known by the name of IDeA.

The Institute of Medicine has been undertaking a study of whether the criteria for IDeA and Experimental Program to Stimulate Competitive Research (EPSCOR) are in fact in need of revision, and we expect that report to be released fairly soon. It would be a good time then to have a conversation with you and others about this issue.

BREAKTHROUGHS IN CYSTIC FIBROSIS

Senator SHELBY. Let's talk about, if we could, the breakthroughs in the research that has been done in cystic fibrosis over the years. We've talked about this before, and there's been some breakthroughs there.

Would you highlight some of them, and how we're doing in that area?

Dr. COLLINS. It's an area of enormous excitement. My own research lab back in 1989 played a role in collaborating with another group in Toronto in discovering the gene for cystic fibrosis. And now, just in the last couple of years, the really exciting fruits of that in terms of drug therapy have emerged with one drug called Kalydeco now approved in record time by the FDA, which shows dramatic responses from individuals who have a particular misspelling of that cystic fibrosis gene.

Unfortunately, only about 4 or 5 percent of cystic fibrosis patients are in that category. But there's great excitement because of phase II and phase III trials now being conducted by Vertex on two new compounds, which should be actually quite useful for 90 percent or more of people with cystic fibrosis.

This all builds upon NIH research that's been done over the decades. It's a wonderful collaboration with the Cystic Fibrosis Foundation in interaction with the company called Vertex. The National Heart, Lung, and Blood Institute, which Dr. Gibbons directs, has funded a lot of this effort through the years. It is a great success story, and one that we hope to replicate for lots of other diseases.

Senator SHELBY. Thank you for sharing it with us.

Thank you, Mr. Chairman.

Senator HARKIN. Senator Cochran.

Senator COCHRAN. Mr. Chairman, I'm pleased to join you in welcoming our distinguished panel of witnesses today.

Dr. Collins, we appreciate your being here again and also coming out into the countryside where we live and work.

Dr. COLLINS. I enjoy that very much, Senator.

Senator COCHRAN. We appreciated the honor of your visit to Mississippi.

And it might interest you to know that just recently, there was an announcement from the Blair Batson Hospital for Children in Jackson, Mississippi, where you were, by a Dr. Hannah Gay, who reported a functional cure of a child who was born HIV positive. And this is news that's getting around the world now and is attracting attention again to the distinction that Mississippi has for people like Dr. Arthur Guyton, who wrote many of your textbooks, and others who have pioneered in research in different areas.

So we look forward to supporting the work that you do, and we hope we'll be able to provide some seed money or incentive grants, funding to ensure that we continue to embark upon daring and innovative approaches to dealing with our health problems in America.

Thank you.

Senator HARKIN. Senator Boozman.

Senator BOOZMAN. Thank you all, and thank you for being here. I really do want to compliment you all as a group. Your efforts, your work, your advocacy really has changed the world, and we appreciate your efforts very, very much.

There's a lot of things that the Government possibly, we could argue, doesn't need to be doing. I think what you all represent is something the State of Arkansas, our communities, can't do individually, and so we do appreciate the work that you do.

PUBLIC ACCESS TO NIH RESEARCH

One thing I'd like to ask about, we have to make some significant decisions here. The agencies have to make some significant decisions. As we have research that is publicly funded, generally, we allow that research to be made available; is that correct?

Dr. COLLINS. Yes, we strongly support the need for that. If the public has paid for the research, the public should have access to it. I think NIH, it's fair to say, has taken the lead in trying to make sure that that kind of access to information happens in a timely fashion.

The recent suggestion, by the Obama administration, is that this kind of policy should be applied broadly across all of the agencies, and I think many are looking at NIH's model as something to replicate in other parts of the Government as well.

DUAL-USE RESEARCH SAFEGUARDS

Senator BOOZMAN. And again, I appreciate that and agree wholeheartedly. And I'm glad that that is the policy.

Can you envision a reason not to do that in some cases?

Dr. COLLINS. Perhaps you're talking about circumstances where the data that's being generated might in fact create some risk to the public if it fell into the wrong hands.

I'm going to ask Dr. Fauci to comment on this, because this often falls in the category of areas that might be amenable to bioterrorist misuse, and we've certainly been engaged in those conversations. And Dr. Fauci has had the lead in many of them.

Tony?

Dr. FAUCI. Yes, thank you for that question.

It is a delicate balance, particularly when you do what is called dual-use research of concern, where the public health imperative for understanding whatever process you're looking at is quite important. Yet you're concerned with two things.

One is the deliberate misuse of things that have to do, for example, with potentially pathogenic microbes that could be used in a bioterror situation or the inappropriate and careless use of that information by people who are not qualified. It transcends all areas of research, but it's particularly acute when you're dealing with the study and perhaps even creation of a microbe that might, in fact, be an issue.

Having said that, we tend, unless there's a really very good reason, to be as open and transparent as possible, because the default rule—and we're careful about that and not careless—is that not allowing knowledge to be generally spread throughout the scientific community has more deleterious effects than the risk of having something being used in a deleterious way accidentally or deliberately by others.

So, it goes along with the concept that Dr. Collins mentioned, that we have been the leaders and we continue to stress the open nature of scientific information.

CLINICAL TRIALS AND VOLUNTEER CONFIDENTIALITY

Senator BOOZMAN. Okay. And as far as we can always put safeguards and a lot of research sometimes involves people and things like that. I mean, we can always put the safeguards in to protect, so that we are able to release the data without jeopardizing people. Is that——

Dr. COLLINS. So, I think there, you're getting at the issue about privacy and confidentiality for people who are part of clinical trials that NIH supports who have been willing to volunteer to take part in a study and who are happy to be part of that, but don't want all of their medical records to be accessible by everybody on the planet.

Yes, we take that with great seriousness and make every effort, and I think we've been quite successful, to keep that information only in the hands of those who have a need to know as part of the research project.

Senator BOOZMAN. Again, thank you all for being here. I really do appreciate your efforts and, as a new member on the panel, I look forward to working with you in the future and supporting your efforts. Thank you.

Dr. COLLINS. We look forward to that, too. Thank you.

IMPACT OF THE BRAIN INITIATIVE ON NEUROLOGICAL DISORDERS

Senator HARKIN. Thank you, Senator.

We'll start a second round here. I wanted to follow-up a little bit on the BRAIN Initiative, Dr. Landis and Dr. Hodes, because when

I first heard about this bump-up in this new initiative, we were talking about it and someone said, well, how is this going to affect all the research on Alzheimer's? I don't know.

There's a report that came out that said that the total cost of care for individuals with Alzheimer's disease will soar from $172 billion in 2010 to more than $1 trillion by 2050; that Medicare costs are increasing more than 600 percent from $88 billion today to $627 billion in 2050, if we keep on the same trajectory.

So, tell me about this BRAIN Initiative. What's it going to do in terms of the research we're doing on Alzheimer's, or is this something separate and apart?

Dr. LANDIS. So, let me talk about the BRAIN Initiative and the promise of the BRAIN Initiative, and then I'll turn it over to Dr. Hodes to address the issue of Alzheimer's.

The long-term goal of the BRAIN Initiative is to be able to develop treatments for patients across the broad range of psychiatric and neurological disorders, and I'll give you a very specific example.

In the case of Parkinson's disease, one of the major advances has been the development of deep brain stimulation where electrodes are planted in particular regions bilaterally of Parkinson's patient's brains in the midcourse of the disease.

This stimulation, kind of like a brain pacemaker, can transform the quality of life of those patients. They can move freely. They're much more active. They would, in some cases, not even appear to have Parkinson's.

That effect wears off with time. This stimulation is very crude. It's an electrode that is influencing the circuit behavior. If we understood more about how the circuits work that control movement, that control compulsions, that control speech, we would be able to design much better interventions, electroceutical interventions—not pharmaceutical, but electroceutical—that would rebuild those circuits in a much more effective way.

Deep brain stimulation is now being used for obsessive-compulsive disorder. It's being used for intractable depression. And in each case, the electrode is going in a different part of the brain, but it's the same crude stimulation.

So, just by analogy to Parkinson's, if we understood the circuits for obsessive-compulsive disorder or intractable depression, we would be able to come up with much more effective ways to change the circuitry to ameliorate those diseases.

IMPACT OF THE BRAIN INITIATIVE ON ALZHEIMER'S DISEASE

Senator HARKIN. That's all well and good, but we have a crisis on our hands with Alzheimer's, a real crisis. And I'm wondering—this is well and good. I'm all for that. But I'm concerned that we're not doing enough to really focus more research on, if you can just put off the onset of Alzheimer's for 5 years, that would save so much money.

So tell me how this affects Alzheimer's research?

Dr. HODES. Thank you for the opportunity to comment on this.

As noted, the cost, the public health and human suffering cost of Alzheimer's, is huge. In addition to the public health demand, of course, what is important is for us to assess scientific oppor-

tunity and quality of science. It's one thing to recognize a problem. Now we have a responsibility to address it in the best possible way.

And the most responsible way to do this at this point, when we don't know what ultimately would be the successful approach, is to invest across a spectrum from those basic discovery on through translation.

So, we have some enormously important and innovative clinical trials happening. In the last year, for the first time, we're able to identify people at enormously high genetic risk, in whom we can find, by bio-imaging, signs of disease years, even decades, before onset and begin for the first time to treat them.

So, we have new opportunities we didn't have before.

But having said all this, we still have an opportunity, and, in fact, an obligation to better understand the cellular and molecular underpinnings, so that we can continue the effort to generate new generations of investment. That is where this BRAIN Initiative happens.

It's clear that Alzheimer's disease is not a disease of just a single cell or even a single cell type. It involves defects in the communications between cells, and the more we understand, in the sense of what the brain will tell us, the better we can intervene to the specific things that are going wrong in Alzheimer's disease.

Senator HARKIN. So, again, you're both telling me that this BRAIN Initiative does have an impact on Alzheimer's research.

Dr. LANDIS. Yes. So, one very surprising finding of the last couple of years has been that there is abnormal electrical activity, almost like mini seizures in the brains of Alzheimer's patients. It's not clear the extent to which that abnormal activity influences the course of the disease.

But if we knew better how to modulate activity in circuits, and which were the right circuits, we could potentially intervene in those electroform activities in Alzheimer's patients and potentially have a very positive effect on their quality of life.

Dr. HODES. It's well-described, and in fact, it comes back to another point made, the concern we have about not being overly conservative, that we don't fail to take advantage of truly bold and innovative new approaches. This is an example, at the same time we're doing the best we can to translate what we think is the best information about cause and potential interventions for Alzheimer's, we still have an obligation to make sure we examine broadly the kinds of information which will tell us about whole new approaches that may be, in the end, the best or most definitive solution.

Senator HARKIN. Thank you all very much.

Senator Moran.

CARDIOVASCULAR DISEASE

Senator MORAN. Mr. Chairman, thank you.

Dr. Gibbons, cardiovascular disease is the leading cause of death in the United States. It's certainly a driver of healthcare expenditures. I'm told it costs the U.S. consumer, the patient, $312.6 billion a year.

Sunday's New York Times had an article on an NIH study that is using genetic sequencing to find factors that increase the risk of

heart disease beyond the usual suspects of high cholesterol, high blood pressure, smoking, and diabetes.

Would you tell us more about that study?

Dr. GIBBONS. Well, thank you for that question. This is one of the great success stories, I think, in biomedical research, where discovery science related to the pathways that determine low density lipoprotein (LDL) cholesterol, the bad cholesterol metabolism, led to Nobel Prizes for Brown and Goldstein.

There was a great public-private partnership that led to the identification of a target that would lower LDL cholesterol. That led to a drug, Statins. I suspect, for those of us over 50, a lot of us in this room may even be on one.

That was a breakthrough drug that's transformed medicine. Indeed, that public-private partnership is one that is critical to advancing medicine.

The question now is that although we have studies that show the remarkable improvements of having patients on statins, unfortunately, there are still patients on statins who have a heart attack every few moments in this country. So, that tells us there's still unfinished business. There's still some unsolved mysteries.

That article related to us continuing to try to figure out those patients where we don't really understand all the risk factors, all the predictors of who's going to have a heart attack. And as you saw in that article, a devastating impact on a whole family that we really couldn't explain, but that's where we have these unprecedented opportunities.

With new technologies, we're able to sequence parts of the genome and probe into why is this family so different and distinctive in a way that's really devastating to it? We're hopeful that that will identify new pathways that will tell us more about the risk of heart attacks. That may recapitulate that story we just had with LDL cholesterol.

That's the promise of the future. Those are the investments we need to make now for those breakthroughs tomorrow.

Senator MORAN. Is there enough research to give us a clue as to what those other factors may be?

Dr. GIBBONS. Well, there's a lot of promise. Perhaps one example, a sort of a harbinger of that, relates to a molecule called proprotein convertase subtilisin/kexin type 9 (PCSK9), in which a similar sort of strategy delved into the molecular determinants of, again, a group of families, a group of patients that had an abnormal level of LDL cholesterol. The probing use of modern genomic technologies unveiled this new gene in this other pathway that told us another potential target.

And indeed, as part of the recapitulation of that public-private partnership in which discovery science translated into drug development, a new drug has been developed that targets that same sort of pathway. That's now in the midst of clinical trials, to see if on top of statins or in a complementary way going after this new target can actually give us more bang for the buck.

Similarly, one of the things that we're learning is that although you have that bad cholesterol, what we're also appreciating is not just that clogging of the arteries but it's also the activation of the

body's immune system that sort of turns against the blood vessel and inflames it just like your allergies flare up your sinuses.

In that sense, the blood vessels were inflamed.

So, what we're now looking at is new targets that may not only target the cholesterol level but that inflammatory response that also promotes heart attacks. That's where some of the great breakthroughs, I believe, are coming. And indeed, we're funding a study that's looking at tackling that inflammation part of the story, to see if we can make the next breakthrough.

Senator MORAN. I wish you great success.

Dr. GIBBONS. Thank you.

ACCESS TO CLINICAL TRIALS

Senator MORAN. Dr. Collins, I have very little time left, but as people know, Kansas is a very rural State. I have concerns about clinical trials.

And in order, I assume, for a clinical trial to have validity, it takes a wide range of demographics and characteristics. And it seems to me there are barriers toward some people joining clinical trials based upon geography, age, other demographic and personal characteristics, perhaps fear of Government research, lack of awareness of clinical trial availability.

What can I do—what is NIH doing—but what can I do as a Senator in caring for Kansans to make certain they are aware of the opportunity to participate in clinical trials and potentially improve their health and save their lives?

Dr. COLLINS. It's a great question. NIH is by law, in our clinical trials, required to be sure we are reaching out to a diverse population. We track that carefully, and all the individuals who review clinical trial grant proposals and the program staff who follow those, make sure that we have a diversity of population involvement in the studies, whether it's heart disease, diabetes, cancer, whatever.

But of course, we are dependent upon public knowledge about the ability to be part of such trials, and I appreciate your question very much in that regard.

There is a Web site called clinicaltrials.gov, which is heavily utilized in every clinical trial that we support. And most of the ones supported by industry are also listed on that site. You can search it very readily to identify a particular condition, in some particular part of the country, where a trial is currently enrolling patients and what's the nature of that trial. And people can decide if they want to take part.

Getting the word out about that would be a wonderful thing to do, and I appreciate very much your suggestion of helping with that. We would welcome that.

Dr. LANDIS. If I could just add something. The National Institute of Neurological Disorders and Stroke (NINDS) recently set up a phase II clinical trials network called NeuroNEXT, with 25 sites across the country. One of them is at the University of Kansas Medical Center, and we are hoping to incorporate into the clinical trials undertaken by that network telemedicine, which would enable, for example, for stroke where patients at a distance to be seen

by and treatment recommended or randomization recommended through the main NeuroNEXT site.

So we're very interested in engaging in this with you.

Senator MORAN. I like that answer. Thank you very much.

Senator HARKIN. I'm sure you do.

Senator Shelby.

PROGRESS OF THE PROVOCATIVE QUESTIONS INITIATIVE

Senator SHELBY. Thank you, Mr. Chairman.

Dr. Varmus, last year, we discussed a new initiative that you started to answer what we call provocative questions in cancer research.

When budgets are constrained, we need, I believe, out-of-the-box ideas to answer some of the big research questions that could lead to the next breakthrough. You're in the forefront and I think your project is an innovative approach to define some of the unanswered questions in cancer research.

Would you share with the committee this afternoon some of the progress you've made on this initiative, and what provocative questions have been awarded grants, or where are you?

Dr. VARMUS. Thank you, Senator.

Obviously, this program is only a little over a year old, so we don't have results yet, but we do have results of advertising for applications.

The first year, we chose 24 questions, the kinds of questions that were raised vary dramatically from questions about why people with profound obesity have increased risk of dying of certain kinds of cancer. There were questions about why drugs that are not all that effective in many circumstances, like chemotherapy for certain kinds of cancer, are remarkably effective for testicular cancer and certain other rare cancers.

We've asked questions about behavior. Why do people still smoke when they know how bad smoking is?

There were 24 questions of those similar dimensions chosen. We've received 750 applications to try to answer those questions. All 24 questions were addressed by at least several of the applications.

Funding is short. We were able to fund slightly over 50 applications. The funded grants address most, but not all, the questions.

We then revised the questions, included some new ones that had come from recent workshops. We reconfigured some questions that we thought, perhaps, could be addressed more effectively if we rephrase them. And we received, this year, so far, several hundred applications.

So, there is obviously a pent-up need. How good the applications are? It's hard to say. Many received very high marks from the reviewers. How well they'll do, that's always a crapshoot, frankly. And we won't know for a few years how well this works.

We have gotten, of course, a lot of feedback from our community. They like the idea that we're not dictating the questions. The questions are coming from a community effort.

We're trying to support the community at a period when morale is poor because of the low success rate. We're trying to say, we are partners in trying to develop the kinds of questions we think this

community should answer, the kinds of risk we should be taking. We see this as one of the ways, not the only way, by any means, in which we try to cope with sequestration, with reduced opportunity to get grants.

Thank you for the question.

AUTOIMMUNE DISEASE RESEARCH

Senator SHELBY. Dr. Collins, I'd like to talk about autoimmune and the research there.

The NIH and various investigators have come a long way in dealing with autoimmune research, because it goes to the basis of so many things. In particular, where are you today in trying to deal with lupus? We've talked about this before and there have been some breakthroughs there. And where do you think you might go?

Dr. Varmus, do you want to get into that?

Dr. VARMUS. No, thank you.

Senator SHELBY. Okay, okay. Any of you could. Dr. Collins.

Dr. COLLINS. Actually, I'm going to ask Dr. Fauci to get in on this, because he's a card-carrying immunologist, and he can really talk about this.

Senator SHELBY. Doctor, thank you very much.

Dr. FAUCI. It's a pleasure. Thank you for the question. One of the approaches that we and other institutes are taking with regard to autoimmune diseases is making some significant advances in the field of what we call immune tolerance.

Immune tolerance is to train the body's immune system not to respond inappropriately against certain antigens. In the case of lupus, those are self-antigens, and that's the reason why they call it autoimmunity.

Several years ago, we established an immune tolerance network that was originally established to look at ways that we could prevent the rejection of transplants. We've expanded that now into the study of a number of other diseases that are clearly characterized by autoimmune phenomenon, including type 1 diabetes, certain allergies, as well as very important rheumatologic diseases like systemic lupus erythematosus.

So, it really is, again, another, I think, beautiful example of studying the fundamental, basic research on the immune system that is now being translated into therapies to suppress inappropriate immune responses.

COLLABORATION WITH INDUSTRY

Senator SHELBY. Dr. Collins, do you want to talk about any therapies that are coming along?

Dr. COLLINS. I appreciate the chance to respond. I just want to mention one collaboration that's underway right now, which is actually quite groundbreaking and, I think, innovative. And that is something called the target validation consortium, which is a group that has come together between industry and NIH to try to identify amongst a wealth of new potential drug targets that have emerged from basic science studies, things like genomics and immunology, which are the ones that are actually going to work, because the industry wants to put their bets on something that's actually going to lead to a drug that's safe and effective.

So, working with industry, we've identified four areas of great opportunity. One of them is autoimmune diseases—rheumatoid arthritis, lupus, Crohn's disease. The others are type 2 diabetes, Alzheimer's disease, and schizophrenia.

And right now, we're in the midst of the design phase of this effort with 10 companies that have agreed to sign up. This is at the very high level with the companies in the design phase. And, if it looks promising in the next couple of months, we're likely to see a major new kind of collaborative effort where industry and NIH agree that this is actually open access, precompetitive information, we can all work on this together. Let's find the most appropriate targets and then turn industry loose to find that next generation of drugs.

Senator SHELBY. Thank you very much.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator.

Senator Mikulski.

Chairwoman MIKULSKI. Thank you.

You know, if we just stuck with the A words, it would keep us all very busy for three lifetimes, from arthritis to Alzheimer's to allergies and so on.

So it's great to hear both sides of the aisle talking about the same thing.

I want to come back to Dr. Fauci.

Senator Shelby, I was also going to raise the question of autoimmune. I'm glad that you did.

MULTIPLE DRUG-RESISTANT BACTERIA

But I want to raise, Dr. Fauci, with you the superbug problem, because this is a significant issue. And I'd like to know where are we heading with our research? What are your thoughts and recommendations? Is it also recommendations that should be implemented in more quality initiatives in hospitals, like the Pronovost checklist?

Could you share with us, because this is a really significant issue that we're hearing from both constituents and hospitals?

Dr. FAUCI. You're very correct, Madam Chairwoman, that the issue of multiple drug-resistant bacteria, and we'll just concentrate on them now as opposed to other types of resistant microbes, are a very important problem in the United States and worldwide, and a growing problem.

If you look at the number, up to a million hospital-acquired infections, of which a rather substantial proportion of them are resistant to the standard drugs leading to the unnecessary deaths of people in the hospital. This is a major public health issue.

There are two approaches to that. One is a public health approach, which really relates to some of the recommendations of our own Centers for Disease Control and Prevention, and the other is the basic research approach, which we at the NIH are taking.

The public health approach is on things like isolation, identification of people when you transfer from one hospital to another to make sure you let people know that you're transferring somebody with a resistant microbe. You know, we had a problem at the NIH a-year-and-a-half ago that we luckily solved. One of the things we

learned is that you have to make people aware of when you're dealing with a drug-resistant microbe in a patient. Washing hands, all kinds of isolation procedures.

But the real core problem, that we've been intensively addressing over the last couple of years, is the lack of a really robust pipeline of new drugs that could take the place of the drugs that are now—to which the microbes are resistant.

So, if you look at how things work with the NIH and how we interdigitate with industry, we generally do the fundamental basic concepts. We make the initial discovery, proof of principle, then maybe go into a phase I or maybe even a phase II trial. Whereas industry, which is responsible for making the product, generally meets us halfway or so.

The risk, economically, for a company to invest a lot of money into the development of new antibiotics is such that we have to help what we call de-risk them. In other words, pushing the envelope closer to getting better understanding of mechanisms of drug resistance, how you can target on a microbe, new targets for drugs to make it easy for the company to get involved in providing us with this robust pipeline.

I think that's going to be a very good approach, because we've actually just recently established a new clinical trial network for multiple drug resistant bacteria in our hospitals.

So again, to reiterate, it's a very serious problem, and at the NIH, we're taking it very seriously.

Chairwoman MIKULSKI. Well, first of all, that's promising to hear. And we also have to look at the role of the Centers for Disease Control and Prevention (CDC) here.

I know, Mr. Chairman, you'll be holding a hearing on that in a matter of days.

But, Dr. Collins, is that, I know it's not the—but is this the methodology you're talking about where you work with the industry on what, I used the term precompetitive, or whatever is the right legal term. But, really because there was so much risk in some of these areas, the private sector is not going to get into it, and we do create our own valley of death, because we don't go far enough. Is this one of those endeavors?

Dr. COLLINS. You're quite right. The valley of death in this situation, that Tony was just describing, can be broad and yawning because the far side of it is even further away, because of companies' lack of really commercial motivation to get engaged.

You develop a drug for highly resistant organism. People will say, you shouldn't use that drug, except in very specific circumstances. Otherwise, you'll use it up and it won't be any good anymore. So the market is very small.

Chairwoman MIKULSKI. And people want cheap antibiotics, too.

Let me get to another thing before my absolute time is up. I know you've talked about Alzheimer's and many issues.

AUTISM

I want to talk about autism, another A word. This is really another epidemic that has hit our family, our family of fellow Americans.

Just about in every school, almost now in every extended family, there is a child facing one of the aspects of the spectrum of autism.

Could you share with us where we're heading with research on this? Is this something we should also look at beefing up? Could you share with us where we are on this? Whoever is appropriate, for anyone.

Dr. COLLINS. I'll say one sentence, and then ask Dr. Landis to say more.

One area that is making progress is to understand genetic contributions to autism. We now think maybe 15 to 20 percent of cases are the result of new misspellings in DNA that were not present in either parent but appear in that child.

Almost always that seems to be in a pathway that involves synapses in the brain. That seems to be the common thread here about what's wrong in autism. The connections between nerve cells aren't forming in the way that they normally should.

But there's much more to say here.

Dr. LANDIS. So, I think that is in fact one of the most promising avenues, and there are a number of genetic studies, which are looking at trios where the parents are normal and the child has autism, and using advanced genetic techniques, identifying the genes that affect the gene or genes responsible.

What's particularly interesting is, as the number of genes go, just as Dr. Collins said, these are genes which act on the development of connections and the development of the synapses. Of most interest is the fact that the same genes are being identified in epilepsy and schizophrenia and a number of other neurodevelopmental disorders.

It will be very important to figure out, first of all, what those mutations do to development, but also why the phenotype of patients, each of which has the same mutation, is so different. So, very interesting, very interesting clues.

Dr. COLLINS. Just to quickly point out also that despite the advances in genetics, we know that's not at all the whole story. There must be profound influences that are based upon other environmental events, some of them probably happening during pregnancy. There's a great deal of intense effort to try to understand that as well.

Chairwoman MIKULSKI. Thank you very much, and just thank you for what you do every day. Thank all the 18,000 people at NIH and the extramural people.

Senator HARKIN. Thank you, Senator.

Senator Boozman.

INTER-AGENCY COLLABORATION

Senator BOOZMAN. Thank you, Mr. Chairman.

Dr. Collins, I'd like to ask about, and really use two very different examples, about the ability of NIH to perhaps work with the other agencies.

I'm on the Veterans Affairs Committee. Everybody at the panel here is very, very concerned about veteran suicide. They're working really hard to try and do something under a lot of pressure to perform.

One of my concerns is the easiest thing to do, if you have a caseload that is bigger than you can handle, there is a tendency to overmedicate. I think that is a problem.

But aside from that, again, the ability of your agency to come in, recognizing there is a problem. They're spending a lot of money in trying to solve the problem.

If there's an effort that we could collaborate, and you all use the unique expertise that you have to help with that problem.

The other thing is I was at the toxicological lab in Pine Bluff of the FDA. And another very differing example is the nanotechnology, which the FDA is concerned about, we're all concerned about. What really helped me grasp it was the fact, when you look up, you can think of infinite upness. With nanotechnology, you're really dealing with infinite smallness, which is amazing.

And as you guys know better than anyone, as you get very small, then everything changes.

But it is something that offers tremendous potential. One of these things that truly can change the world by helping us not use as much resources by better lubrication, things like that where things don't wear out, these conflict minerals and things.

So is there the ability for you all to step in and help FDA deal with those kinds of problems and support the work at the toxicological lab?

Dr. COLLINS. Senator, those are two terrific questions.

With regard to suicide, I think all of us are deeply concerned to see what the rates are of suicide, especially in returning servicemen. We've been working, actually, closely with the Department of Defense in a program called Study To Access Risk and Resilience in Servicemembers (Army STARRS), which has enrolled more than 100,000 recruits, trying to identify what, if any, kind of warning signs have been missed in the past that could give us a better chance to intervene before suicide occurs.

This is a close collaboration between our National Institute on Mental Health (NIMH) and the Department of Defense. And there is an interaction there also with the Department of Veterans Affairs (VA) because of their very strong interest in the same issue.

With regard to your question about toxicology——

Senator BOOZMAN. I'm sorry, the next step again would be dealing with people that are actually at that point.

Dr. COLLINS. Yes.

Senator BOOZMAN. That might be helpful also.

Dr. COLLINS. Indeed. And of course, suicides are more common than homicides in this country, and there is a great deal of effort to try to understand ways to identify risks.

Obviously, for people who have not been in the military, if you look at what are the risk factors for suicide, bipolar illness is a very major correlate, because when people with that condition go into a deep depression, that is often where the risk is highest.

Senator BOOZMAN. And heavily medicating in some cases makes it worse or better?

Dr. COLLINS. I think the experience has been that proper medication, with Lithium and other efforts, can be lifesaving. Reading books by Kay Jamison, for instance, would emphasize that, as

someone who has written about it and who has experienced it herself.

But there are challenges in terms of getting it just right, and we are still working on new interventions that will be more effective than what's currently available, because most of the drugs have been around quite a long time, and it's time to see if we could find some new answers. This notion of working with industry to find new targets comes to mind.

With regard to your question about toxicology and nanotechnology, Peggy Hamburg, who's the commissioner of the FDA and I jointly run a leadership council that tries to identify ways that our agencies can work closely together, particularly helping FDA with identifying new regulatory science opportunities, and FDA helping NIH identify areas where more science is needed and where our investigators can be better prepared to conduct trials that FDA can then review.

Nanotechnology is a very interesting example, because there is a question about the safety of nanotechnology applications for human health. Given that this isn't exactly a simple area, all different particle sizes, all different kinds of compound constitution, NIEHS, the National Institute of Environmental Health Sciences, has a research program on this. And we are part of the National Nanotechnology Initiative.

We mentioned earlier the BRAIN Initiative, trying to come up with ways that could sample these 86 billion neurons. If we're going to get anywhere near that, we're going to need nanotechnology tools to do so. So, it is very much an appropriate question. To be sure, we're working together.

Senator BOOZMAN. Thank you, and again, thanks for all you do.

NIH/CDC/FDA COLLABORATION ON H7N9 (AVIAN FLU)

Senator HARKIN. The last question Senator Mikulski asked, I think Dr. Fauci, the question about the superbugs. One last thing was that in meeting with Dr. Frieden of the Centers for Disease Control and Prevention a few days ago, talking about this new avian flu.

You've been down that road before, Dr. Fauci.

So, a new one has popped up. This one is known as H7N9, and there have been 131 confirmed cases by the World Health Organization (WHO), 32 deaths. There has been no evidence of sustained human-to-human transmission.

But the problem is, as I understand it, that there is obviously a very high death rate, but the birds that are infected have no symptoms. And so again, how are you correlating research on this along with the CDC?

Dr. FAUCI. Thank you for that question. It's a very good example of very nice collaboration and coordination between the different agencies of HHS, not only CDC and NIH, but also FDA.

So, where we are right now, there are actually 35 deaths. There were three deaths that were reported yesterday and today. So it's 131 cases and 35 deaths.

We are approaching this exactly the same way as we approached the H5N1 that started in 2003 that we discussed before this committee many times that's still smoldering, as well as the 2009

H1N1 real pandemic that we had. That is virtually within days of noticing this, the virus was isolated, sequenced, sent to the CDC with the sequence, who are then, by reverse genetics, created what we call seed viruses for the development of a vaccine.

A seed virus is a virus that we make that we can then distribute to the different pharmaceutical companies that we have contractual relationships with for our regular seasonal flu. They are already starting to make what we called pilot lots to determine whether or not we're going to be able to test these.

The NIH, which is our main responsibility, has already developed and designed clinical protocols to test what is the right dose, do you need an adjuvant or not, do the doses differ between children, adults, elderly, and pregnant women. I've seen the trial designs and they are ready to go. As soon as the pilot lots are up, which will likely be by the end of June, the beginning of July, we'll start clinical trials.

Now, we may not ever have to use the vaccine. But the important thing is, we'll get those lots, we'll know how to use it. So, if it does begin to have what you mentioned correctly, sustained human-to-human transmissibility, which it does not have right now, if it does, then we can scale up and have a vaccine available.

We've also done many of the sequencing to look for genes that might predict whether it's sensitive or resistant to the neuraminidase inhibitors, the ones we commonly use, Tamiflu and Relenza. Fortunately, they appear to still be sensitive to those antivirals.

UNIVERSAL INFLUENZA VACCINE

Dr. COLLINS. So, Tony, wouldn't it be great if you didn't have to do this every time a new strain appeared? Do you want to say something about progress to get a universal influenza vaccine, because that's quite exciting? We might not have to have this conversation in 10 or 15 years.

Senator HARKIN. How close are we to that?

Dr. FAUCI. Well, you know, I can't give you a time, but I can tell you we're clearly closer than we were a year or two ago, and let me explain why. Because, what Francis is alluding to, for people who didn't hear it, is the universal flu vaccine that you could actually give to someone and then it would be inducing protection against a wide range of influenza strains, from season to season, and even from pandemic to pandemic.

What was discovered a few years ago by NIH grantees, that there's a part of the protein that's the main protein of influenza called hemagglutinin that is shielded from the immune system recognizing it.

So, when you get infected, Mr. Chairman, or you get a vaccine every year, your body's immune system doesn't recognize a part of that protein that doesn't change from strain to strain. The part that changes is called, well it looks like a mushroom, it's got a head and it's got a stalk. The part that's the protective part is the head, and it changes from season to season. And when you have a pandemic, it changes a lot.

So, if you make an immune response, you're good for that season, but you're not good for the next season when it changes. Whereas

on the stalk of the hemagglutinin, there is a sequence, a particular protein, that doesn't change from flu to flu. So, we've now figured out a way, how to show the immune system that particular protein, so that it makes an immune response against it. We've now shown it in animals, mice, ferrets, and monkeys, that when you show them this protein, they make antibodies against the wide array of influenzas.

We started phase I trials, showing that it's safe, and it induces a response. We're getting ready to go into a phase II trial.

So, I can't give you a year when we're going to have it, but we're a heck of a lot closer than the last time you asked me that question.

Senator HARKIN. I had no idea of that. That's pretty encouraging. I mean, just think of the health implications.

Dr. FAUCI. That would be enormous.

Senator HARKIN. It would be huge.

Dr. FAUCI. Right.

Senator HARKIN. And the savings in illnesses, the hospitalizations, loss of work, my goodness, plus just knowing that you're safe against some of these pandemic flus.

Dr. FAUCI. And you could stockpile. See, that's the thing that we can't do. We're always in a yearly race. We find out what's going to be circulating, and we race to make a vaccine to be ready in the fall to give to people, so they can have it for the winter.

If you have a universal flu vaccine that essentially covers it all, you can start making it right now for 2 years from now.

Senator HARKIN. Of course. Keep us informed.

Dr. FAUCI. I will.

Senator HARKIN. That's very encouraging. Especially if you've got something that you know dosage-wise you can do for children, adults, pregnant women, all the different types of people that need this type of a vaccine.

Dr. FAUCI. So, when you come to the NIH, we'll show you where it's done.

Senator HARKIN. I will, thank you. That's very encouraging.

Senator Moran.

EXPERIENCED AND NEW INVESTIGATOR FUNDING

Senator MORAN. Mr. Chairman, thank you.

Just a brief question, Dr. Collins. I'd like to have you assure me that there are actions in place that make certain that both well-established investigators are funded as well as incubator-type environments where young investigators can thrive and provide great breakthroughs.

Dr. COLLINS. Of course, that's very important. It could hardly be more important.

I think the most important resource we have is the talented scientists who do the work, and some of them are in mid-career and just incredibly at the top of their game, and others just getting started with vision and drive and energy.

The sad story is that all of those groups are taking a hit right now. There's nobody getting protected.

We do what we can, particularly with early stage investigators to be sure they have a chance to get started. So, we have them,

in the way we do our peer review, compete against each other. The early stage investigators, they don't have to compete in the same pool as far as funding decisions with somebody who already has an established lab and a lot of preliminary data and a lot of publications, because we want to be sure that we're not disadvantaging our future, which are these folks that are just getting started.

But there is no magic here when success rates have fallen for everybody to 15, 16 percent. I know we are losing significant talent all through the career range of the people that we support, from the young to the middle, to those who are basically in the cap of their career.

DECLINE IN THE NUMBER OF NEW INVESTIGATORS

Senator MORAN. You have the statistics—I've never seen you not be able to answer a question, so I know you have the statistics. Are the numbers of new applicants, individuals who have never applied, or organizations that have never applied for a grant, is that number changing?

Dr. COLLINS. You know, I'm a little concerned to see that this year, the numbers seem to be dropping back a bit, and that's actually quite troubling. That begins to suggest that people are beginning to lose hope. And you can sort of see why.

When investigators, with this success rate of 15 or 16 percent, spend most of their time just writing a grant only to have it rejected, but then they'd better be writing another one, otherwise, their lab is going to close.

They don't get to do science that much anymore. It's all about trying to find the funding from the Government, from foundations. I think, after a while, as people begin to burn out with that, perhaps we are seeing a fall off in the willingness to go through that experience over and over again only to see rejection.

So, I am concerned, as one of the warning signs that the community is beginning to be sufficiently disheartened as we're going to lose people.

We have lots of anecdotes about that. It's hard to collect precise data about exactly how many investigators have given up. We're in the process of trying to do that, but the anecdotes are sufficiently numerous that I'm deeply worried.

Senator MORAN. Well, Doctor, I would never contradict you, but I find this hearing always a place of hope. And it is one of the places within the halls of Congress in which, when you leave the hearing, you have a better outlook for what the future holds.

And so I appreciate very much what you and your team, what the folks at NIH and those that you fund and support, provide something that America desperately needs, something called hope.

And I just would encourage you to let Dina Faddah know that there is hope, and tell her that we all encourage her to pursue that career in research and science and medicine. And that while there's always challenges, the opportunity to provide hope to Americans, to provide hope to the world, it's worth the battle. And we look forward to being allies with her in that effort to see that hope continues.

Dr. COLLINS. Senator, that's wonderful, and I will personally pass that word of encouragement to her.

Senator MORAN. Thank you.
Senator HARKIN. Thank you, Senator.
Senator Shelby.

VETERAN SUICIDE

Senator SHELBY. I want to follow up on the troubling information we have about so many veterans committing suicide when they come back from Iraq or Afghanistan, and the devastation it does to the families, to the society and so forth.

My question is this, I don't know if you have it, I don't know if the VA has it or DOD, but are there statistics, say, going back to the end of the Second World War, about the number of veterans coming back, the number of suicides per thousand, the Korean war, the Vietnam war, the conflict in Iraq and so forth. Because that would be very troubling, yes, but maybe informative, too, to a point.

Do you know if they have those statistics, Doctor?

Dr. COLLINS. I'm sure there are such statistics. I don't have them at my fingertips. And of course, one would have to look at the statistics with some caution in the fact that in the past, anyway, oftentimes suicides were not reported as suicide, because of the stigma attached to that. So, it could well be that one looks at those and it looks as if——

Senator SHELBY. That could be skewed.

Dr. COLLINS. Yes, they would be skewed, particularly in the past and probably still in the present, where suicides, because they do carry for families——

Senator SHELBY. Soldiers go through this awful stress in combat.

But as a society, we need to figure out how to prevent it, don't we?

Dr. COLLINS. I totally agree with you. And again, I think if Dr. Tom Insel were on this panel, who is the director of the National Institute of Mental Health (NIMH), he would immediately put forward to you a number of things that our Mental Health Institute is trying to do in terms of identifying risk factors and interventions, figuring out how this fits together with things like traumatic brain injury and post-traumatic stress disorder (PTSD).

Senator SHELBY. Thank you very much.

Thank you, Mr. Chairman.

Dr. LANDIS. I think one of the differences between Iraq, Afghanistan, or in earlier wars are the improvised explosive devices with significant repeated mild traumatic brain injury. There's evidence that it's an invisible wound, and soldiers often don't recognize that this has been an issue and don't seek appropriate help.

So, I think that the statistics for these wars might be different than previous wars.

Senator SHELBY. One added dimension, I just thought of it, because so many of our soldiers have had multiple tours—some volunteered, some didn't, in all this—which puts a lot of stress on them and their families.

Maybe there are studies into that, too, say one tour, two tours, three tours, and dramatic effects.

Dr. COLLINS. Yes, I'm quite sure that data has been looked at by the Department of Defense and is part of the effort as we're identi-

fying risk factors in this STARRS study that ought to be looked at very carefully. And if there is some indication that the number of tours is a factor, obviously one would want to intervene in a prospective way to try to provide that kind of support that apparently is not currently sufficient.

FUNDING THE FUTURE OF NIH

Senator HARKIN. Thank you, Senator Shelby.

Well, again I want to thank you all for your dedicated public service, your leadership in health.

It's been my privilege and pleasure to have either chaired or been the ranking member of this subcommittee since 1989. So I worked with some of you for a long time.

And every time we have you all up here for NIH, again, it's just again a reminder, I think to all of us, that there's just certain things we can't back down from. We made so many great strides in health research, keeping people healthy, their cancer rates. Everything else has been phenomenal, especially in childhood leukemia. It's been remarkable.

And with the Human Genome Project, we now have some keys that we've never had before, the new technologies that we have that we can use now. It just seems that this is the time to redouble our efforts to increase significantly the funding for NIH.

How do you do that? Well, there seems to be an attitude, I'm not saying anybody in particular, that we want something for nothing. If you want the best, it costs something, in terms of the best scientists, the best brains, the best technologies, the best equipment. We've always been the best in biomedical research in this country.

I'm afraid that we are falling way behind, so we've got to find sources of funding.

Back in the early 1990s, Senator Mark Hatfield was the chair of this committee. And I was ranking member at that time, and he was on this subcommittee. This was one of his devotions as it is Senator Mikulski's now.

And we came up with a proposal. I don't know if it was his idea or my idea.

But the basis of it was this, that when you buy a drug, when you go out to your pharmacy and you buy a drug today, some of that money goes for research. But when you buy a health insurance policy, none of that goes for health research.

So our idea then, and this was about the time, I think, when we're working on the Clinton proposed health bill and stuff like that, we came up with a proposal, Hatfield and Harkin, and that was to have every health insurance policy that you would have a certain amount, percentage of each one that would then go to the NIH.

It would come through this committee. And it was only just a few cents, a couple, 2 or 3 cents, I think, on the dollar.

And then someone pointed out, well, but if you do that, then that would just supplant what you're doing on the discretionary money. So, okay, what we'll do is we'll say, okay, it will go into like a trust fund for NIH, but it can only be accessed as long as the Congress appropriates at a minimum what they did last year, plus an inflation factor.

Dr. FAUCI. That's a good idea.

Senator HARKIN. Well, yes, thank you.

Well, we tried. We kind of pushed that along for a while. We got some pushback, obviously, from the health insurance industry, I understand that, and others.

But then that whole thing sort of faded out and nothing was done on it.

Now with this new healthcare system, Obamacare, coming along, there's going to be 35 million more people having health insurance policies in this country. Some of them subsidized by the Government, others not.

I just wonder if it's not time. I ask my friends here to revisit this and to think about some new source of funding like that.

Yes, the ultimate payer will always be that individual person out there, because their health insurance payment will go up a little, 2 or 3 cents on the dollar. But they'll have the satisfaction of knowing that little increase is going to go for only one thing. That's NIH research.

It can't go anywhere else, and it can only go as long as Congress appropriates what we did last year plus an inflation factor.

Somehow, we've got to come up with this funding. Anybody else got a better idea, the door is open. I am willing to look at anything. If anybody's got a better idea, let me know about it.

Senator SHELBY. Mr. Chairman?

Senator HARKIN. Yes.

Senator SHELBY. Did you do some work as to how much money that would raise?

Senator HARKIN. Oh, yes. It was quite significant.

Senator SHELBY. It would help a lot?

Senator HARKIN. Oh, big time. And it was just a couple of cents on the dollar, was all, when you think about it. And now we're going to have a lot more heath insurance policies out there.

And I talked to some of my health insurance carriers, and we have a lot of health insurance carriers out there.

Well, you know, I suppose they could live with it, but it wasn't high on their agenda. But again, it's just something I think we ought to roll around.

And like I said, anybody else here in the audience or anybody else listening got any better ideas, let me know.

But we've got to get more funding for NIH. We can't continue to go down this road. I got 20 months left here, 19 months left here. I'd like to see this turned around.

ADDITIONAL COMMITTEE QUESTIONS

Obviously, I'd like to see us start the doubling process again, but that won't happen. I understand that. But finding a new source of dedicated revenue that will be there and that we know will be there year after year after year, that's got to happen so that these young researchers, the one you're talking about, it's nice to give her a pat on the back and say follow your dreams. Yes, I back up what Jerry said on that.

But there's got to be something there to make sure that those dreams are realizable, and that funding has to be there.

So, yes. Then we need to go on, but I just think this is something we've just got to address.

So the record will remain open for 7 days for additional statements or questions for the record.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED TO DR. FRANCIS S. COLLINS

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

Question. Dr. Collins, last month was the 10th anniversary of the completion of the Human Genome Project, which you led and, I'm happy to say, came in ahead of schedule and under budget. What have we learned from this effort and where are we going?

Answer. To gain perspective about how the field of genomics has advanced since the Human Genome Project (HGP), it is illustrative to compare the "state-of-the-art" at the beginning of the HGP in 1990, at its completion in 2003, and now, in 2013. For instance, during the HGP, it took 6–8 years of active sequencing and approximately $1 billion to generate that first reference sequence of the human genome. In 2003, that same feat would have still required 3–4 months and $10–50 million. But today, a human genome can be sequenced in approximately 1–2 days for a mere $3–5 thousand. As the time and cost of human genome sequencing have plummeted, the power of genomic strategies and the volume of generated genomic data have increased profoundly.

This capacity to generate more data through improved and less expensive technologies has enabled researchers to interrogate genome structure and function and learn how the genome contributes to health and disease. For example, in 1990, we knew of approximately 50 genes that, when mutated, caused a human disease; in 2003 that number was almost 1,500; and today, it is nearly 3,000. Further, knowledge about the genomic bases for our different responses to medications—an area of science called pharmacogenomics—also has grown steadily. In 1990, only four Food and Drug Administration (FDA)-approved drugs required labels that pointed out the relevance of a patient's genomic makeup for that medication; by 2003, that number had increased to 46; and today, it stands at 106. In fact, genomic contributions to medical research have been so substantial that fully half of "Time" magazine's "Top 10 Medical Breakthroughs in 2012" reflected genomics accomplishments, and these were in large part supported and/or facilitated by National Human Genome Research Institute (NHGRI) research programs.

During the last decade, building on the discoveries of the HGP, we have learned much more about how the genome functions and how genomes differ from person to person. For instance, in 2012, the ENCyclopedia of DNA Elements (ENCODE) project funded by NHGRI published a landmark series of papers reporting a catalog of functional elements within the human genome. The ENCODE catalog is like a GPS map for the human genome—just as by zooming in on a GPS map of the United States (to find the location of points of interests like banks and gas stations), the ENCODE catalog is now routinely used by researchers worldwide to zoom in on regions of interest in the human genome that are important for their studies.

Meanwhile, the 1000 Genomes Project, funded in part by NHGRI, has led to a much greater understanding of the variation among human genomes. By sequencing the genomes of more than 2600 individuals from different populations across the world, the project is identifying patterns of variation between individuals and populations that will help advance understanding of the genetic factors contributing to many common diseases. To date, the 1000 Genomes Project data have been used in published research studies focused on autism, Alzheimer's disease, cancer, cardiovascular disease, and cirrhosis.

The field of genomics is now focusing increasingly on the links between genomic variation and disease—and how that knowledge can be applied clinically. Genomic medicine is being used to advance certain medical specialties such as oncology, where genomics-based diagnostic methods are increasingly being used for cancer screening and for guiding treatment strategies. Examples include the widespread use of "BRCA" testing in patients with familial risk factors for breast and ovarian cancer, the use of testing to predict breast cancer recurrence, and the use of genomic diagnostic tests to determine the suitability of particular therapeutic treatments. Findings being generated through the work of The Cancer Genome Atlas—a re-

search program co-funded by NHGRI and the National Cancer Institute—are confirming that cancers that appear to be morphologically similar can be separated into distinct subtypes based on genomic information, thereby informing the choice of therapies. Establishing the specific mutations that drive the growth of a patient's tumor can prevent the needless and costly use of harsh chemotherapeutic drugs that are ineffective for that tumor subtype. From less complex diagnostic tests that predict the effect of trastuzumab (Herceptin®) use in breast cancer, vemurafenib (Zelboraf®) use in melanoma, or crizotinib (Xalkori®) use in lung cancer, to more advanced strategies of sequencing a tumor's mutated genome as a means to guide treatment, genomic medicine is becoming a powerful tool for guiding clinical care.

Beyond cancer, genomics is also fueling major strides in other clinical areas. For instance, National Institutes of Health's (NIH) Intramural Undiagnosed Diseases Program applies genomic analyses to cases where a diagnosis has proven elusive to medical experts. To date, through the program, two new diseases have been discovered, and 50 patients have received long-sought diagnoses. Similar approaches using genome sequencing to diagnose rare diseases have been used in Wisconsin (Nic Volker)[1] and California (Noah and Alexis Beery),[2] resulting in life-altering treatments for the affected patients. Beyond applications for disease identification or categorization, a promising study at Stanford University showed that DNA sequencing could be used to monitor organ transplant recipients non-invasively to detect early signs of rejection. Another study, also conducted at Stanford University, used genomics to screen a library of existing FDA-approved drugs to determine whether they might be repurposed for use in other diseases. Through this work, the possibility of repurposing an epilepsy drug for use in ulcerative colitis and Crohn's disease, and using an anti-ulcer drug to treat certain forms of lung cancer, has been highlighted.

It is worth noting that although the primary aim of the HGP was to improve health, the project's effects have not, and will not, be confined to the clinic. A report by Battelle Technology Partnership Practice (Battelle) published in 2011 showed that the HGP has had a very positive impact on the United States economy.[3] Specifically, the report estimates that between 1988 and 2010, Federal investment in genomic research generated an economic impact of $796 billion, particularly impressive considering that HGP spending between 1990 and 2003 was only $3.8 billion. The report further found that in 2010, the genomic sector directly supported more than 51,000 jobs, indirectly supported more than 310,000 jobs, created $20 billion in personal income, added $67 billion to the United States economy, generated more than $3.7 billion in Federal taxes, and generated more than $2.3 billion in State and local taxes. An updated report is being published by Battelle on June 12th.

Question. Dr. Collins, a Council of Councils working group recently recommended that NIH retire all but 50 chimpanzees to a sanctuary, in response to an Institute of Medicine report on research involving chimpanzees. Are you likely to accept that recommendation? If not, why not? Are there any issues or road blocks to moving the chimpanzees?

Answer. On January 22, 2013, a working group of the Council of Councils presented its report to the Council on the Use of Chimpanzees in NIH-Supported Research. The report recommended that, among other things, "The majority of NIH-owned chimpanzees should be designated for retirement and transferred to the Federal sanctuary system" and that "A small population of chimpanzees [approximately 50] should be maintained for future potential research. . . ." The same day, the Council of Councils accepted these and 26 additional Working Group recommendations, and transmitted them to NIH for consideration. NIH subsequently issued a request for comments and, after considering the public comments, accepted most of the Council recommendations on June 26, 2013.

With respect to the recommendation that advises that NIH retire the majority of NIH-owned chimpanzees, a vast majority of the commenters agreed with this recommendation. However, a number of commenters noted that the funding limits of the Chimpanzee Health Improvement Maintenance and Protection (CHIMP) Act of 2000 may affect the agency's decisions about retiring chimpanzees no longer needed for research. The CHIMP Act amended the Public Health Service Act to establish and maintain a system of sanctuaries for the lifetime care of chimpanzees that were used in research that the Health and Human Services (HHS) Secretary (through NIH) designates as no longer needed for research. Prior to accepting the Council

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[1] See: http://www.jsonline.com/features/health/111224104.html.

[2] Bainbridge MN et al. "Sci. Trans. Med", June 15, 2011 Whole-Genome Sequencing for Optimized Patient Management. http://www.ncbi.nlm.nih.gov/pubmed/21677200.

[3] Tripp, S. "Economic Impact of the Human Genome Project" (Battelle Technology Partnership Practice: 2011).

recommendation, there were already 219 chimpanzees living in, or were scheduled to be relocated to, the Federal sanctuary system. Three-hundred sixty (360) additional NIH-owned chimpanzees are not retired and reside outside the sanctuary system.

Despite overwhelming public support to retire most NIH-owned chimpanzees, three issues need to be addressed before NIH could fully implement the recommendation to retire the majority of NIH-owned chimpanzees: (1) restrictions on funding levels in the CHIMP Act (often referred to as the cap), (2) lack of capacity in the Federal sanctuary system, and (3) limits in authority to manage the sanctuary system.

FUNDING RESTRICTIONS IN THE CHIMPANZEE HEALTH IMPROVEMENT MAINTENANCE AND PROTECTION ACT

The CHIMP Act authorized HHS to establish the sanctuary system but includes a technical provision that currently limits the amount of its financial resources that HHS (through NIH) can provide for: (1) care and maintenance of the chimpanzees within the Federal sanctuary system; and (2) construction to establish the system. NIH believes that its authority to use appropriated monies to fund the Federal sanctuary system expires once the funds spent for the operation and establishment of the sanctuary system reach $30 million. As of February 2013, NIH had spent over $29 million in Federal funding on the sanctuary system and expects to reach $30 million early in fiscal year 2014. After that, HHS may lack the authority under the CHIMP Act to obligate additional funding to the Federal sanctuary system for care and maintenance of the chimpanzees within the Federal sanctuary system as well as future construction to expand the system. General Provision language has been proposed in the fiscal year 2014 President's budget request to remove this restriction.

CAPACITY

The agency agrees that the majority of chimpanzees that NIH owns could be eligible for retirement but additional capacity in the Federal sanctuary system is needed. Although the contractor (Chimp Haven, Inc.) that maintains the Federal sanctuary system plans to use private funding to construct additional space to house 110 chimpanzees from the New Iberia Research Center, these new areas will not be sufficient to accommodate the majority of NIH-owned chimpanzees that the Council recommended retiring. NIH is currently unable to support construction at the sanctuary due to funding restrictions in the CHIMP Act. Without additional construction or the authority to support such work financially, NIH understands that the Federal sanctuary system will be unable to accept additional chimpanzees until the current sanctuary population declines.

LIMITS IN AUTHORITY TO MANAGE THE FEDERAL SANCTUARY SYSTEM

NIH believes the CHIMP Act also limits the HHS Secretary's authority to expand the Federal sanctuary system by adding additional compliant retirement facilities. Currently, the system is composed of only one sanctuary that is now at capacity, but several facilities have approached the agency with an interest in accommodating retired chimpanzees. NIH would like to consider additional facilities to add to the system so long as they conform to CHIMP Act requirements and the implementing of sanctuary regulations.

To add additional sanctuaries to the Federal system, the CHIMP Act requires the HHS Secretary to seek approval from the Board of Directors that oversees the nonprofit entity that runs the Federal sanctuary system. This provision, consequently, could limit the Secretary's ability to retire chimpanzees to other potentially compliant retirement facilities that could provide a cost savings or less expensive option. HHS believes it should be able to retire chimpanzees directly to other facilities if the Secretary determines the criteria in the law are met. We would like to point out that it would not incur additional costs to retire chimpanzees into an expanded sanctuary system. Funds to support their care in the research facilities could be transferred for their care in the sanctuary system. Alternatively research facilities could be modified to qualify for participation in the Federal sanctuary system. Although NIH agrees that the majority of its chimpanzees could be designated for retirement and transferred to the Federal sanctuary system, NIH is not in a position at this time to implement the recommendation.

QUESTIONS SUBMITTED BY SENATOR MARY L. LANDRIEU

Question. A year ago, our Nation adopted a National Plan that set as goal one treating and effectively preventing Alzheimer's disease by 2025. This plan was required under the National Alzheimer's Project Act, bipartisan legislation approved unanimously by Congress in 2010. Achieving this goal will not be easy. In the past several months, at least three industry trials testing potential therapies for Alzheimer's have reported disappointing phase 3 study results.

Based on what you know today, how confident are you that the Nation will achieve the 2025 goal of preventing and treating Alzheimer's disease?

Answer. The identification and development of interventions that will prevent or treat Alzheimer's disease have proven to be extremely challenging, and it is still not possible to predict with certainty when an effective treatment or preventive intervention will be available. However, we have greater reason than ever before to be optimistic.

Our efforts have been significantly advanced by recent breakthroughs in biomedical imaging that are enabling us to identify and track the earliest pathological stages of the disease process, long before clinical symptoms are apparent. These discoveries, in addition to discovery of other early biomarkers of the Alzheimer's disease process, have opened a "window of opportunity" for us to target and potentially reverse the disease's underlying pathology before cognitive, behavioral, and emotional symptoms appear. National Institutes of Health (NIH) has begun to launch its first such clinical trials in presymptomatic individuals. For example, in one high-profile study, investigators are studying whether an antibody treatment, crenezumab, which is designed to bind to and possibly clear away abnormal amounts of amyloid protein in the brains of people with Alzheimer's, can prevent decline in cognitive function. Crenezumab is being tested among members of a unique and large family population in Colombia sharing a genetic mutation known to cause observable signs of Alzheimer's disease at around age 45, along with a smaller number of U.S. participants ages 30 and older. We anticipate initial results from this groundbreaking study by 2017.

NIH also supports more than 35 Alzheimer's disease clinical trials, including a number of studies of interventions to slow disease progression among individuals who are already showing symptoms. More than 40 compounds are currently under study to stimulate and advance research on the discovery and development of new preventive and therapeutic interventions for Alzheimer's disease (AD), mild cognitive impairment, and age-related cognitive decline.

Question. What level of funding for Alzheimer's research at the NIH do you think is needed to maximize our chances of achieving this goal, and what other measures can our Nation take, recognizing these fiscally challenging times, to stop this disease?

Answer. NIH has made one-time internal re-allocations to the Alzheimer's disease budget in fiscal year 2012 ($50 million) and fiscal year 2013 ($40 million) that have made it possible to develop new opportunities in critical priority areas. Sustained availability of funds, as indicated in the fiscal year 2014 President's budget request, would further facilitate targeted initiatives in high-priority research areas. Under the fiscal year 2014 President's budget request, NIH currently estimates it would spend a total of $562 million on Alzheimer's disease research.

In the current challenging budget climate, we are continuing to take a number of steps to leverage our resources to the maximum extent possible. For example:

—We have developed a rigorous and inclusive process for soliciting expert advice on research priorities, most notably through the May 2012 Alzheimer's Disease Research Summit, at which internationally recognized experts in the field met to formulate an integrated multidisciplinary research agenda that will accelerate the development of successful therapies for AD across the disease continuum. Summit participants also identified the types of resources/infrastructure and new public private partnerships that will be necessary to successfully implement this research agenda.

—We have created the International Alzheimer's Disease Research Portfolio, a unique database of nationally/internationally funded AD research, which will enable organizations around the world to coordinate funding strategies and leverage resources in order to maximize the impact on public health and avoid duplication of effort and inefficiency.

—We have conducted an in-depth analysis of the NIH Alzheimer's disease research portfolio and tied specific milestones to the goals of the National Plan to Address Alzheimer's Disease.

—Where appropriate, we are coordinating efforts with private funders and advocacy organizations and actively pursuing public-private and international partnerships.

Question. With respect to the level of funding at the NIH for Alzheimer's disease, I would like for you to address what appears to be an unacceptable gap between the growing costs of this disease to the Nation and the amount of our Federal investment. More than 5 million Americans are estimated to be suffering from Alzheimer's disease, a number that is expected to more than triple by 2050. If the prevalence and trajectory of the disease remains unchanged, the total costs associated with Alzheimer's disease will near or exceed $1 trillion annually by mid-century.

Answer. In fiscal year 2012, the total NIH expenditure for Alzheimer's disease research was approximately $503 million, an increase of approximately $55 million, or 12 percent over fiscal year 2011. This reflected a one-time $50 million increase allocated to NIH Alzheimer's research for fiscal year 2012. In fiscal year 2013, NIH is also allocating $40 million of funds within the Office of the Director's budget to Alzheimer's research. For the fiscal year 2014 President's budget, NIH estimates it will spend a total of $562 million on research related to this disease.

It is important to recognize that while Alzheimer's research continues to be of tremendous importance to NIH, it is one of a number of highly compelling priorities that include research on diabetes, heart disease, cancer, mental illness, as well as cross-cutting research affecting discovery in multiple disease areas. NIH maintains a careful, rigorous, and ongoing planning and priority-setting processes to ensure an appropriate balance of resources in basic, clinical, and translational research, with the ultimate goal of safeguarding the health and well-being of all Americans.

Question. A recent RAND Corporation study published in the New England Journal of Medicine estimates that the direct healthcare costs associated with Alzheimer's disease are $109 billion annually, exceeding the direct care costs associated with cancer and heart disease. When costs of informal caregiving are factored in, annual costs of Alzheimer's and dementia skyrocket and are estimated today to be as high as $215 billion annually. Alzheimer's is the most expensive disease to American families and taxpayers—more expensive than HIV AIDS, Heart Disease and Cancer. Despite the recognized scope of this crisis, NIH is spending approximately $480 Million on Alzheimer's research

How do you explain this disparity between the growing societal burden and economic threat posed by Alzheimer's and the very small investment we are making at the NIH in Alzheimer's research?

Answer. In fiscal year 2012, the total NIH expenditure for Alzheimer's disease research was approximately $503 million, an increase of approximately $55 million over fiscal year 2011. This reflected a one-time $50 million increase allocated to NIH Alzheimer's research for fiscal year 2012. The National Institute on Aging (NIA) funded over $335 million in Alzheimer's disease research—approximately one third of the Institute's research budget. For the fiscal year 2014 President's budget, NIH estimates it will spend a total of $562 million on research related to this disease.

Alzheimer's research continues to be of tremendous importance to the NIH and the NIA. The number of individuals with Alzheimer's disease continues to increase, and our efforts to identify an intervention that will prevent or treat the disease have borne disappointing results. However, Alzheimer's disease is one of a number of highly compelling NIH priorities that include research on heart disease, cancer, mental illness, and diabetes, as well as cross-cutting research that informs discovery in multiple disease areas. Both NIH and NIA maintain careful, rigorous, and ongoing planning and priority-setting processes to ensure an appropriate balance of resources in basic, clinical, and translational research, with the ultimate goal of safeguarding the health and well-being of all Americans.

Question. Do you agree that Alzheimer's research deserves funding that begins to approach the scope of the problem it poses? If you agree that there is a problem here, please provide specifics on how you intend to address this vast disparity in funding within the authorities you have available to you today.

Answer. In this challenging budget climate, we are continuing to take a number of steps to leverage our resources to the maximum extent possible. For example:

—We have developed a rigorous and inclusive process for soliciting expert advice on research priorities, most notably through the May 2012 Alzheimer's Disease Research Summit, at which internationally recognized experts in the field met to formulate an integrated multidisciplinary research agenda that will accelerate the development of successful therapies for AD across the disease continuum. Summit participants also identified the types of resources/infrastructure and new public private partnerships that will be necessary to successfully implement this research agenda.

—We have created the International Alzheimer's Disease Research Portfolio, a unique database of nationally/internationally funded AD research, which will enable organizations around the world to coordinate funding strategies and leverage resources in order to maximize the impact on public health and avoid duplication of effort and inefficiency.
—We have conducted an in-depth analysis of the NIH Alzheimer's disease research portfolio and tied specific milestones to the goals of the National Plan to Address Alzheimer's Disease.
—Where appropriate, we are coordinating efforts with private funders and advocacy organizations and actively pursuing public-private and international partnerships.

Question. I have a longstanding interest in and commitment to improving the health of all Americans. The research activities at NIH play a critical role in this issue. The National Institute on Minority Health and Health Disparities (NIMHD) at NIH only has a budget of approximately $200 million, paling in comparison to other NIH Institutes and Centers (ICs) like Human Genome Institute with $500 million or the National Cancer Institute at $5 billion. I stand for elimination of health disparities to be a national priority—and for it to be funded like one. The NIMHD's budget should be increased to fulfill this mission.

As you know, the RCMI program within the NIMHD is responsible for developing and enhancing the research infrastructure of minority institutions and directly fosters the development of new generations of minority scientists. I am disappointed to see the nearly $6.5 million decrease from fiscal year 2012 funds being requested for the Research Centers in Minority Institutions program.

Can you please tell me the rationale in the decreased funding for this important program?

Answer. The Research Centers in Minority Institutions (RCMI) program provides resources for several critical areas of support for biomedical, clinical, behavioral, and social sciences research. Infrastructure development creates a foundation for the research enterprise through renovation/alteration of new research facilities and the development of specialized research support capabilities such as biomedical informatics and research design/biostatistics expertise. Activities under the RCMI program broaden the opportunities to conduct clinical and translational research through collaborative projects with an emphasis on improving minority health and reducing health disparities. In addition, instructive training and mentored research training experiences for early-stage investigators interested in health disparities research facilitate career advancement for junior faculty members.

The RCMI program was transferred to NIMHD in fiscal year 2012 with the dissolution of the National Center for Research Resources (NCRR). At the NCRR, the RCMI program was one of the Center's main programs aimed at addressing minority health and health disparities. Consistent with its mission, the NIMHD's program portfolio is exclusively focused on improving minority health and eliminating health disparities. Integrating the RCMI program into the NIMHD has been a priority for the Institute over the past year. This integration means taking a strategic look at the Institute's priorities, plans, and the overall portfolio, with the goal of balancing our scientific research investments, particularly since the RCMI program is programmatically similar to other NIMHD congressionally mandated programs. In so doing, the NIMHD seeks to ensure that priorities, programs, and resources are appropriately aligned consistent with its mission, as well as the mission of the NIH; the changing pace of science and the health disparities environment; and that duplication in efforts are identified and reduced; therefore, a reduction in funding for the RCMI program and other NIMHD programs was proposed for fiscal year 2014. NIMHD is committed to the goals and objectives of the RCMI program, and to fully integrating the program into the Institute in a manner that fosters collaboration and partnership between RCMI and other NIMHD/NIH programs, and provide opportunities to enhance the program's contribution to the Institute's mission, as well as the health and well-being of the Nation.

Question. The National Center for Advancing Translational Sciences (NCATS) mission includes a commitment to the behavioral sciences but I am concerned that the Center has not taken sufficient action to bring basic behavioral and psychological science discovery into new applied behavioral interventions. A stronger effort is critical to accelerate the translation of basic behavioral research discoveries into broadly disseminated new therapeutics and clinical care products and protocols, particularly in addressing substance abuse, suicide, depression, and similarly urgent public health issues confronting the Nation

Answer. To bring the benefits of science more quickly into patient care, NCATS was formed with the mission to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of

diagnostics and therapeutics across a wide range of human diseases and conditions. NCATS' mission includes strengthening the entire spectrum of translational research—defined broadly to include the early steps necessary to develop new therapeutics, devices and diagnostics from basic discoveries, the steps necessary to establish real world efficacy, and the research needed to improve the practical implementation and dissemination of improved approaches to care.

NCATS is committed to translating basic behavioral and psychological discovery into interventions that have a discernible impact on human health. These interventions can span the translational space of development of a therapeutic, preventive, or diagnostic or addressing the critical areas of implementation, dissemination, or adherence. New methods and technologies are needed in addressing behavioral and psychological interventions as well as greater integration of these approaches in all portions of the translational spectrum.

Many Clinical and Translational Science Awards are already supporting investigators working in these areas through their study design and biostatistical, regulatory, and community engagement resources, as well as with pilot project funds for innovative approaches. For example, the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) provides an enterprise in which NIDA treatment researchers, and community-based service providers cooperatively develop, validate, refine, and deliver new treatment options to patients in Community Treatment Programs (CTPs). The NIDA CTN utilizes the resources of the CTSA program at many of its sites for their studies of new interventions for substance abuse and addiction.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

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.

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.

Premature deaths across the life-span related to CHD are unacceptable, however recent data suggest that the number of infant deaths related to CHD is decreasing. Successful interventions in infancy and childhood are resulting in an aging population of congenital heart disease survivors. How is the National Institutes of Health (NIH) systematically responding to this new population of survivors reaching adolescence, adulthood, and advanced age? How are you utilizing adult congenital heart disease research experts in these efforts? How are you supporting adult CHD experts to grow the field? Is the NIH offering training grants to grow the field? Is the Pediatric Heart Network inclusive to adult CHD experts? Is your agency formally engaging adult populations in CHD research?

Answer. The National Heart, Lung, and Blood Institute (NHLBI) is keenly aware of the medical and research needs of adults with congenital heart disease and is supporting a number of activities to meet these needs.

The Pediatric Heart Network (PHN) is following a cohort of patients, now aged 13–27, who underwent a Fontan procedure, to correct a CHD, earlier in life. Assessments include family functioning, quality of life, neurodevelopment, and access to healthcare as children transition into adulthood.

The Pediatric Cardiac Genomics Consortium (PCGC), whose goal is to understand the genetic basis of congenital heart disease and the contributions of genetics to individual patient outcomes, has enrolled more than 5000 patients with congenital heart disease, 20 percent of whom are adults.

The Health, Education and Access Research Trial (HEART–ACHD), conducted with NHLBI support in partnership with the Adult Congenital Heart Association (ACHA) and the Alliance of Adult Research in Congenital Cardiology (AARCC), found that more than 40 percent of adults with congenital heart disease have a gap in cardiac care of over 3 years, usually during the critical "transition" time from the teenage years into the early 20s. The study investigators also found that these patients responded well to educational interventions, resulting in improved knowledge about their conditions and also about research.

The Research Empowerment for Adult Congenital Hearts (REACH) project, another ACHA–AARCC collaboration, received NHLBI American Recovery and Reinvestment Act (ARRA) funding to demonstrate the feasibility of a patient-centered re-

search model for adults with congenital heart disease and employ electronic health record technology to create a national infrastructure for research.

NHLBI has been exploring the use of global unique identifiers (GUIDs) to link information already collected in a number of different databases on persons with congenital heart disease. PCGC investigators, in collaboration with colleagues at the National Institute of Mental Health (NIMH) who developed the GUID software, have begun a pilot to assign GUIDs to enrolled patients. If successful, GUIDs will be rolled out to PHN studies and registries that enroll patients with congenital heart disease such as the Society for Thoracic Surgery Registry.

NHLBI staff responsible for adult and pediatric cardiovascular disease research meet regularly with adult congenital heart disease experts and ACHA representatives to advise them about NIH research opportunities generally, discuss relevant NHLBI activities, and provide input into specific research proposals from the community.

NHLBI supports several research training and career development programs that focus on various aspects of congenital heart disease in adults, including adherence to treatment and medical outcomes. The Institute recently developed a PHN Scholars award to fund small pilot studies and encourage young investigators to conduct research in congenital heart disease. One of the awards, titled "The Clinical Significance of Abnormal Spirometry after the Fontan Procedure," will enroll adult participants in the PHN cohort study mentioned above. The young investigator's primary mentor directs the Boston Adult Congenital Heart Service.

Question. In May of 2010, the National Cancer Institute (NCI) reported that the likelihood of being diagnosed with gastric cancer at age 25–39 years had increased by almost 70 percent since 1977. There are minimal symptoms of gastric cancer and it is most often diagnosed at a late stage when curative treatment is impossible. The American Cancer Society (ACS) estimates 21,600 new cases of gastric cancer will be diagnosed in 2013 and 10,990 people will die from the disease. According to the NCI, about 80 percent of people with stomach cancer are diagnosed with advanced metastatic cancer. At stage 4, the 5-year survival rate for gastric cancer is four percent.

Please describe what investments are being made by the NCI to improve biomedical discoveries pertaining to gastric cancer. The Cancer Genome Atlas (TCGA) provides a rewarding opportunity to enhance our understanding of gastric cancer through genomic data. What steps is the NCI taking to ensure TCGA data are utilized for gastric research? Further, what steps is the NCI taking to assist gastric cancer researchers in utilizing the TCGA data to translate promising data from the research bench to patient bedsides?

Answer. Most gastric cancers arise from the gastric epithelium and are classified as adenocarcinomas. These are divided into two types, the intestinal type, which develops in the antrum and is usually well-differentiated, and the diffuse type, which develops in the body of the stomach, is poorly differentiated, and usually has a poorer prognosis than the intestinal type. Gastric cancer does not appear to be hereditary in most patients. However, a few with the diffuse type have a hereditary form, arising from an inherited mutation in the E cadherin gene, which encodes a protein that helps the epithelial cells stick together. Most cases of gastric cancer are attributable to infection with the bacterium "Helicobacter pylori (H. pylori)", and progressively stronger evidence suggests that early antibiotic treatment of this common infection in high-risk patients can reduce the risk of developing this cancer.

The expected frequency of gastric cancer in 2013 actually represents a substantial decrease compared to 80 years ago. Since 1930, the incidence and mortality from this cancer have decreased by more than 80 percent. The rates continued to decline during the first decade of the 21st century, according to the 2013 Annual Report to the Nation on the status of cancer, a joint effort of the American Cancer Society, the Centers for Disease Control and Prevention, and the NCI. The report also notes that during this decade, the incidence of gastric cancer decreased about 15 percent for men (who account for about 60percent of cases) and a little under 10 percent for women, while its mortality rate decreased even faster, by more than 30 percent for men and more than 25 percent for women. Nevertheless, gastric cancer remains a formidable disease, with most advanced cases having a poor prognosis. The NCI has more than 80 research projects devoted at least in part to gastric cancer. Several other NIH Institutes, especially the National Institute of Allergy and Infectious Disease (NIAID) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), also support research in this area, with emphasis on "H. pylori".

Gastric cancer is one of the cancers being studied by The Cancer Genome Atlas (TCGA), which is a joint research effort of the NCI and the National Human Genome Research Institute. TCGA is expected to have a major impact on our understanding of the genetic and epigenetic changes associated with more than 30 cancer

types being studied in unprecedented detail in this initiative. Tumor tissues from approximately 325 cases have been collected to date and are being analyzed. Data is expected to be available next year.

In general, TCGA data is being used to refine the diagnosis of cancer, to define and delineate both the heterogeneity and the common features of various cancer types, and to elucidate the molecular pathways that control the malignant behavior of cancer cells, with the long-term goal of improving the outlook for cancer patients. These data are available to qualified researchers through public databases designed to protect patient privacy. The TCGA team provides extensive support to researchers accessing TCGA data, including step-by-step protocols for how to apply and locate TCGA data, as well as preliminary data analysis to those not able to manipulate the raw data. The availability and broad utilization of the TCGA data are demonstrated by the number of publications using TCGA data (to date, already close to 400) and the number of grant applications that include TCGA data (to date, more than 800). TCGA works with investigators and other components of NCI to help apply findings from TCGA to the development of new diagnostics and therapeutics.

The era of targeted treatment of gastric cancer, with research support from the NCI, has begun even before the TCGA data on this cancer become available. One recurring therapeutically relevant theme in cancer is that abnormalities in one tumor type may also be found in other tumor types. In this context, the protein encoded by the ErbB2 gene, which was found initially to be effectively targeted in breast cancer by a specific monoclonal antibody, trastuzumab, has also been found to be overexpressed in some gastric cancers; treatment of these patients with trastuzumab, in conjunction with standard chemotherapy, can increase their overall survival, which has led to its approval by the FDA for the treatment of gastric cancer. Encouraging preliminary results in gastric cancer have also been seen with therapy directed against other molecular targets, such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF).

Prevention is another important NCI-supported area. Research on "H. pylori" has provided insight into the observed differences in oncogenicity among different strains of the bacterium. These basic research findings have clinical implications, as they can identify those patients most likely to benefit from eradication of their "H. pylori" with antibiotics.

We anticipate that the detailed information from TCGA and other research from NCI-sponsored grants will bring new information about the causes of gastric cancer and its pathogenesis, and will identify new molecular targets, leading to continued progress in our efforts to fight this cancer.

Question. In fiscal year 2013 alone, sequestration threatens to cut the NIH's $30.7 billion budget by almost $1.6 billion. This reduction in funding jeopardizes NIH's ability to invest in biomedical research and slows the pace of discoveries. Please summarize the impact of sequestration on NIH's ability to award grants and support the training and education of scientists. Please describe the impact of sequestration on biomedical innovation and how the cuts in funding may impact patients currently enrolled in clinical trials. Are you aware of reports quantifying the ripple effect sequestration has on biomedical research, biotechnology industries, and economic development in the United States?

Answer. Sequestration requires NIH to cut 5 percent or $1.55 billion of its fiscal year 2013 budget. NIH must apply the cut evenly across all programs, projects, and activities (PPAs), which are primarily NIH institutes and centers. This means every area of medical research will be affected. Compared to fiscal year 2012, NIH expects to issue approximately 700 fewer competitive research project grants and admit approximately 750 fewer new patients to the NIH Clinical Center. In addition, NIH will not increase training stipends for National Research Service Award recipients in fiscal year 2013. While much of these decreases are due to sequester, NIH funding is always a dynamic situation with multiple drivers.

The reductions imposed under sequestration have, and will continue to have a negative impact on biomedical innovation and the training and education of young scientists. Medical breakthroughs do not happen overnight. In almost all instances, breakthrough discoveries result from years of incremental research to understand how disease starts and progresses. Even after the cause and potential drug target of a disease is discovered, it takes on average 13 years and $1 billion to develop a treatment for that target. NIH is aware that its research funding directly supports hundreds of thousands of American jobs and serves as a foundation for the medical innovation sector, which employs 1 million U.S. citizens. Cuts to NIH funding will have an economic impact in communities throughout the U.S.

For additional details on the impact of sequestration see: http://www.nih.gov/news/health/jun2013/nih-03.htm

QUESTIONS SUBMITTED BY SENATOR JACK REED

Question. The Congressional Budget Justification for the National Institute of Child Health and Human Development highlights the National Children's Study as an "unprecedented opportunity" to examine factors that affect child health and development. However, the research community continues to raise concerns with the major changes to the design of this landmark study proposed by the National Institutes of Health (NIH).

The NIH is supposed to have a contract in place with the IOM to review the Vanguard Study and new proposals by the end of May. Has that contract been signed?

Answer. The fully executed Task Order for the contract with the Institute of Medicine (IOM) to review the study design for the National Children's Study (NCS) Main Study was signed on May 28, 2013. The period of performance for the contract began June 3, 2013.

Question. What process are you developing in anticipation of the final report next year in order to incorporate the recommendations from the IOM into the methodology for carrying out the Main Study?

Answer. All procurements related to data collection for the Main Study are delayed until after the IOM report is released. The content of those solicitations will be based on the recommendations of the IOM panel, and guided by ongoing public discussions with the NCS Federal Advisory Committee, the Independent Study Monitoring and Oversight Committee, and the Federal Consortium. These groups will meet within the month following the projected public posting of the IOM report in June 2014. The NIH will integrate the IOM recommendations with input from the advisory committees to construct the NCS Main Study, including the Study's methodologies and implementation plan. New solicitations based on the updated design, methodologies, and implementation plan will be published at least 60 days following the release of the IOM report.

Question. Presuming the data already collected could be useful, will researchers have access to the data already collected while the IOM conducts its study? Could NIH provide grants through other programs to use the data that the Federal government already spent $1 billion to collect?

Answer. Qualified researchers, whether or not they are directly associated with the NCS, already have access to the Study data, and will throughout the course of the Study. While we anticipate that many NIH Institutes and Centers may choose to support grants that utilize NCS data and samples, access to NCS data and samples will not require such grants.

Question. I understand that NIH is currently engaged in an internal process to evaluate how it tracks research data on age, gender, race, and other patient identifiers. What is the timeline for completing this process?

Answer. In 2010, the NIH Principal Deputy Director convened an internal task force to evaluate the policies and procedures related to the inclusion of women, minorities, and children. Among the outcomes of the task force was the formation of a new Subcommittee on Inclusion Governance (SIG) in November 2011, co-chaired by Dr. Janine Austin Clayton, Associate Director for Women's Health, and Dr. Alan Guttmacher, Director, "Eunice Kennedy Shriver" National Institute of Child Health and Human Development.

With input from the task force, the SIG is taking a comprehensive look at the NIH policies regarding the inclusion of women, minorities, children, and other population groups in clinical research and clinical trials. The SIG has reaffirmed that the primary goal of NIH inclusion policies is not enumeration, but rather to ensure that the distribution of participants in clinical research reflects the population(s) needed to accomplish the scientific goals of the study. Investigators, reviewers, and NIH staff all have key roles to play in implementing and monitoring the policies.

Data collection on the basis of sex/gender, race, and ethnicity is currently being re-engineered to streamline and simplify the processes and align better with the electronic grant application procedure. We anticipate the new system will be deployed in mid-late 2014. With respect to age, the governance committee is examining how information about age is provided by grant applicants, reviewed during the peer review process, monitored during the period that the study is carried out, and captured by internal NIH systems. In addition, the subcommittee is analyzing the NIH pediatric portfolio to determine what, if any, modifications may be needed to ensure the inclusion of women, minorities, and children in NIH clinical research.

Question. The National Institute of Child Health and Human Development (NICHD) conducts the majority of pediatric research among all of the Institutes, but a substantial portion of the research relevant to children occurs in the Institutes across NIH. For research projects that are not designed specifically for children—

but could possibly be relevant to children—how does NIH work with investigators to determine the appropriate participation of children?

Answer. While the NICHD does support a plurality of the pediatric research funded by the NIH, nearly every NIH Institute and Center (IC) reports annual support for pediatric research. This support comprises new and continuing investigator-initiated pediatric research projects, and projects funded under Funding Opportunity Announcements. These projects are coded using NIH's Research, Condition, and Disease Categorization process, a computerized tool that allows the NIH to provide consistent and transparent information to the public, providing a list for each fiscal year of all NIH-funded projects related to a specific research category: http://report.nih.gov/rcdc/. If a given project is sufficiently related to an area of pediatric research, it will be included in the Pediatric Research category.

NIH also supports a range of mechanisms to foster pediatric research training and career development, and an active pediatric research loan repayment program, which enables qualified health professionals who commit to conducting pediatric research for at least 2 years to receive a substantial repayment of their educational loans. These programs signal to the research community the importance of pediatric research and the commitment of the NIH to fostering this area of science.

On a more individual basis, the NIH peer review process helps researchers to refine and clarify the goals of their research applications or proposals. Reviewers can be helpful in providing guidance to applicants who wish to conduct clinical research, including whether their proposed research includes adequate numbers of individuals from affected populations. Researchers whose projects receive funding then work with NIH program officials during the entire course of the grant or contract, reporting on their progress annually and receiving input from those officials about whether their aims are being successfully met.

Question. What more could NIH be doing to support investigators in pediatric enrollment in their research studies and clinical trials?

Answer. NIH is committed to ensuring that children participate in the full range of NIH research. In fiscal year 2012, NIH pediatric research funding totaled approximately $3.6 billion, including studies in pediatric patients conducted in NIH's intramural research program at the Clinical Center in Bethesda, MD. NIH supports nearly 100 multidisciplinary center and network programs focused on children's health needs. These include the Autism Centers of Excellence, the Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, and the Children's Oncology Group. NIH's Office of Rare Diseases Research and several NIH Institutes and Centers fund the Rare Diseases Clinical Research Network to facilitate collaboration among experts in many different types of rare diseases. NIH works with the FDA to administer the Best Pharmaceuticals for Children Act to support and coordinate pediatric pharmacology research, with the goal of increasing the dosage and efficacy information available about therapeutics used by children. The 60 centers that comprise NIH's Clinical and Translational Sciences Awards include substantial pediatric expertise.

NIH reviews and awards these and other networks and centers programs on a regular basis, usually at about 5-year intervals, ensuring that they are productive and continue to produce the best science. For example, during the coming year, the NIH will post a funding opportunity announcement seeking applications for sites to participate in the ongoing Collaborative Pediatric Critical Care Research Network, which provides the infrastructure to pursue rigorous clinical trials and other studies in pediatric critical care medicine. The eight currently funded sites include pediatric expertise in pulmonology, cardiology, nursing, and other disciplines essential to children's health.

QUESTIONS SUBMITTED BY SENATOR JON TESTER

Question. Most of the research programs that receive NIH research grants are affiliated with an institution of higher education. I encourage you to support non-University and non-hospital affiliated research institutions throughout the country, and in particular to focus on those located in rural America. Academic and non-profit institutions based in rural States consistently receive less funding from the NIH. This oversight is compounded when their work is overlooked by other researchers, regardless of the quality of their science.

Due to a lack of higher education or medical facility affiliation, outstanding research institutions in rural areas often struggle to obtain research support and funding. I am concerned that the bias towards researchers with affiliations is shortsighted and overlooks quality research being done by nimble, independent institutes.

In 2012, the NIH received 63,524 research grant applications. How many of those grant applications were from facilities and researchers not affiliated with an institution of higher education? How many of the grants ultimately awarded went to independent small research institutions?

Answer. In fiscal year 2012, more than 18,500 applications were submitted by organizations that were not institutions of higher learning. Approximately 4,600 of these applications were submitted by nonprofit independent research organizations, and approximately 800 of the applications submitted by nonprofit independent research organizations were awarded grants. Independent research organizations have a success rate that is comparable to those of research hospitals and institutions of higher learning.

Question. How do the sequestration cuts further impact the ability of small research institutions' access to grants? What steps is the NIH taking to mitigate this issue and ensure that smaller institutions can compete with larger institutions?

Answer. NIH's post-sequestration fiscal policy applies similar reductions in funding to all organizations regardless of institution size or type. Investigators from all types of organizations, including small academic institutions and research organizations, often develop collaborations with research personnel at large institutions to gain access to resources that would not otherwise be available to them. NIH encourages these collaborations and works to ensure access to research resources and technologies among its grantees through its sharing policies (http://grants.nih.gov/grants/sharing.htm)

In addition, the Academic Research Enhancement Award (AREA) grant program supports small-scale research projects in the biomedical and behavioral sciences conducted by faculty and students at educational institutions that have not been major recipients of NIH research grant funds. Eligible institutions are institutions of higher education that do not receive more than $6 million per year in NIH support in each of four of the last 7 years. NIH remains committed to the AREA grant program in the face of budget restrictions.

QUESTIONS SUBMITTED BY SENATOR JEANNE SHAHEEN

Question. Diabetes and its complications significantly impacts our Nation's health and economy. In fact, new estimates show that the disease costs our Nation $245 billion annually, a 41-percent increase from 2007. It is the number one cause of end-stage renal disease (ESRD), which is the largest driver of Medicare costs at $29 billion in Medicare in 2009.

I understand that tight blood sugar control can cut in half the incidence of ESRD and could save Medicare over $126 billion in 25 years. Given this personal and economic toll on our Nation, how is National Institutes of Health (NIH) prioritizing diabetic kidney disease? What, if any, are some new insights into the prevention and treatment in the area of kidney disease?

Answer. There is no known way to restore kidney function once it is lost, but treatment can usually slow or prevent degradation of kidney function if diabetic kidney disease is detected early. Therefore, prevention and early detection of kidney disease are important research priorities. At the NIH, the Institute with the primary responsibility for supporting research related to diabetes and kidney disease is the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and many of the research efforts included below have been supported by this Institute.

The NIDDK's Diabetes Control and Complications Trial showed that intensive blood glucose control reduces risk of complications of the kidneys, eyes, and nerves of people with relatively recent onset type 1 diabetes; the U.K. Prospective Diabetes Trial established that careful blood glucose control provides similar benefit to people with recent onset type 2 diabetes. The NIDDK's Diabetes Prevention Program clinical trial moved that prevention effort one step earlier, even before the onset of diabetes. It found that people at risk of developing type 2 diabetes can prevent or delay disease onset and improve their blood sugar through an intensive diet and exercise intervention, or, to a lesser degree, with the diabetes drug metformin. In cases where people receiving the lifestyle intervention actually progressed to develop type 2 diabetes anyway, their diabetes was found to be easier to control, and to confer a lower risk for complications.

Despite these efforts to proactively and aggressively manage diabetes, the risk for end-stage renal disease (ESRD) in patients with chronic kidney disease (CKD) associated with diabetes remains high. Moreover, among the larger population of people with CKD who have not progressed to ESRD, cardiovascular disease poses a significant burden. The NIDDK's Chronic Renal Insufficiency Cohort (CRIC) Study, which

started in 2001, is a prospective observational cohort study of approximately 4,000 men and women and is the largest cohort study of CKD yet undertaken. The objectives of the Chronic Renal Insufficiency Cohort (CRIC) Study are to improve understanding of the relationship between CKD disease and cardiovascular disease and to examine traditional and non-traditional risk factors for progression of these diseases. An emphasis was placed on recruiting participants at high risk for ESRD, including persons with diabetes (about one-half of the study participants), African Americans (also about one-half of the study participants) and Hispanic Americans. Important scientific findings are emerging from this study. For example, fibroblast growth factor 23 (FGF–23) is a growth factor that regulates phosphate metabolism. Elevated FGF–23 was shown to be an independent predictor of risk for ESRD in patients with relatively well-preserved kidney function. FGF–23 may turn out to be a useful biomarker to predict risk of adverse outcomes in patients with CKD. In a separate study, increased levels of FGF–23 were associated with an indicator of cardiovascular disease. CRIC Study investigators have also found a strong association between eye disease and levels of kidney function, suggesting that eye disease may reflect underlying CKD. In addition, the increased burden of cardiovascular disease in Hispanic Americans with CKD has been documented. These and other findings from the CRIC Study in the coming years are expected to inform clinical trials and clinical management practices to reduce the burden of ESRD in the U.S.

The NIH is also seeking to improve the translation and implementation of treatment approaches to kidney disease and diabetes in a real-world setting. This research seeks to identify factors that lead to the adoption, maintenance, and sustainability of science-based interventions at the practice level, where they can have an immediate impact on patients' lives, such as improving blood pressure control, improving laboratory measures of metabolic control or nutritional status, and/or changes in kidney function. Looking forward, the NIH recently asked the community to identify research objectives that would improve our understanding of basic kidney function and aid in the prevention and treatment of impaired kidney function and prevention of progression to ESRD, welcoming interested parties to submit, discuss, and prioritize ideas via an interactive Web site. The approaches identified may aid in the discovery of new therapies, the identification of regulatory pathways, the generation of animal models for preclinical work, and the development biomarkers with clinical utility so that diabetic kidney disease patient outcomes can be improved.

Question. Over the past few years, I have been concerned that the level of funding for NIDDK in the President's budget proposals has not kept pace with the rate of biomedical inflation and the growing diabetes epidemic, threatening the ability of NIDDK to continue to make progress on promising diabetes research.

Would you please share the percentage of grants that NIDDK has been able to fund over the past 2 years and how this will affect grants/research going forward?

Answer. In fiscal year 2011 and fiscal year 2012, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) used 81 and 80 percent of its regular appropriations, respectively, to fund new and continuing grants supporting the biomedical research enterprise at sites around the country. This support includes research project grants, research centers, careers, other types of research support, and research training awards for individuals and institutions. In those two fiscal years, the NIDDK sustained a success rate for funding research project grants—which receive the majority share of grant funding—of 21 and 20 percent, respectively. These data reflect a combined success rate for funding research project grants supported by the NIDDK's regular appropriation and the Special Statutory Funding Program for Type 1 Diabetes Research. The success rate is defined as the percentage of reviewed grant applications that receive funding, and is calculated for the fiscal year. In fiscal year 2013, we expect that the success rate will decline somewhat due to the loss of funds through sequestration. At the President's budget request level for fiscal year 2014, the NIDDK anticipates a success rate for funding research project grants of 22 percent. These relatively stable success rates for research funding are enabling NIDDK to continue to foster progress and new advances in diabetes.

Question. Would you also please share how the Administration plans to ensure that there is a strong investment in the NIDDK in fiscal year 2014 that will lead to breakthrough discoveries and ultimately a cure of diabetes?

Answer. The President's fiscal year 2014 budget request reflects a strong commitment of the NIDDK to support research tackling diabetes and its devastating health and economic consequences. For example, the funds requested for fiscal year 2014 will enable the NIDDK to continue major diabetes clinical trials, such as a recently launched multicenter study of the comparative effectiveness of four common drugs used for treating type 2 diabetes, and a new trial testing vitamin D for type 2 diabetes prevention. The fiscal year 2014 budget request will also enable NIDDK to pur-

sue emerging opportunities in the study of diabetes risk genes in minority populations, which could lead to new therapeutic approaches. These resources will also support NIDDK's plans for research that can lead us to personalized medicine for diabetes—for example, the Institute plans to support research to elucidate how an individual's genetic makeup affects his or her response to anti-diabetic medications, such as metformin. Under the President's budget request, the NIDDK will continue to fund translational research in fiscal year 2014 and support health information dissemination activities to bring scientific discoveries in diabetes to real-world medical practice and other community settings. NIDDK plans for fiscal year 2014 also include advancing research on brown fat—an exciting new area of study with therapeutic potential—and moving forward with major studies of gestational diabetes. Moreover, the NIDDK investment in diabetes research is augmented by the research activities of the many NIH Institutes, Centers, and Offices with an interest in diabetes and its complications, which will also continue in fiscal year 2014. All these efforts will be further enhanced by fiscal year 2014 mandatory funds from the Special Statutory Funding Program for Type 1 Diabetes Research, and the NIDDK will convene an expert panel on June 6–7, 2013, to obtain external scientific and lay input on future research directions to be pursued with these funds.

Our plans for fiscal year 2014 are contingent upon Congressional action, but we are hopeful that the fiscal year 2014 investment in diabetes research, spearheaded by NIDDK, will continue to lead us toward new discoveries, new therapies, and possibly cures for diabetes.

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

Question. As a follow-up to my questions at the hearing on the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, I understand that the National Institutes of Health (NIH) is currently working on a scientific plan for this program. However, I remain concerned that we have no details on how much funding would need to be provided in the coming years. Could you please provide the subcommittee a 10-year budget estimation, both for the overall mapping project and NIH's share in particular.

Answer. It will be imperative that cost estimates be strongly informed by a rigorous scientific planning process. NIH has charged a high-level advisory group with developing a plan for the NIH BRAIN Initiative, which is to include timetables, milestones, and cost estimates. As part of this process, members will consult the scientific community, patient advocates, and the general public to ensure that this plan is informed by stakeholder input. Interim recommendations are expected late this summer and final recommendations are anticipated in the summer of 2014. This plan will be publicly available and widely shared with both the public and with BRAIN Initiative partners.

Question. As the lead institution, do you foresee NIH's funding role being increased in future years?

Answer. It is anticipated that as the BRAIN Initiative gains momentum, additional funds may be needed to support promising areas of research. The pace at which NIH's role might grow in future years will depend on the relative competing priorities and the overall availability of funds at that time.

Question. Will NIH be expected to be the primary funding agency in future years?

Answer. At this time, each funding agency is undertaking an extensive scientific planning process to identify their specific areas of focus and to define their potential investments in the BRAIN Initiative. Given that NIH has such a substantial investment in neuroscience research, it is certain that we will remain a leader in advancing the goals of the BRAIN Initiative.

Question. Can you specify the role you see each Federal agency taking in this initiative?

Answer. In general, NIH will develop new tools, training opportunities, and other resources. The Defense Advanced Research Projects Agency (DARPA) intends to explore applications—such as a new generation of information processing systems and restoration mechanisms—that dramatically improve the way we diagnose and treat soldiers suffering from post-traumatic stress, brain injury, and memory loss. The National Science Foundation (NSF) has expressed a commitment to supporting research that spans physical, biological, social, and behavioral sciences. Moving forward the agencies will work in close collaboration to ensure that their efforts are complementary and leverage the unique missions of each; ultimately catalyzing an interdisciplinary effort of unprecedented scope.

Question. What role do you expect private research institutions to play in the project?

Answer. Currently there are four private partners involved in the BRAIN Initiative: the Allen Institute for Brain Science, the Howard Hughes Medical Institute, the Salk Institute for Biological Studies, and the Kavli Foundation. Each partner will support areas of research in which they are best positioned to advance the overarching goals of the BRAIN Initiative. The Allen Institute for Brain Science, a nonprofit biomedical research organization, is a leader in large-scale data generation, for example, mapping gene expression in mouse, monkey and human brains and public sharing of data and tools. The Howard Hughes Medical Institute, the Nation's largest nongovernmental funder of basic biomedical research, has a focused investment in developing and disseminating new imaging technologies for use in model organisms. The Kavli Foundation will encourage the application of nanotechnology to neuroscience.

Question. Is it your goal to expand the public-private partnership for this initiative in the future?

Answer. NIH's first goal is to develop a rigorous scientific plan for the BRAIN Initiative that is sufficiently informed by a broad and inclusive process. After the scientific plan is established, NIH will continue to seek ways to leverage public-private partnerships.

Question. What would happen if each of the proposed agencies does not provide the requested amount in fiscal year 2014?

Answer. The NIH Director recognizes the tremendous opportunity of the BRAIN Initiative and is committed to ensuring its success. In the event that funds are not provided for this Initiative, NIH will continue to support smaller aspects of this project that continue to advance neuroscience research. However, the scale of this project might be minimized in comparison to the President's bold vision of truly "revolutionizing" our understanding of the human brain.

Question. The goal of the Institutional Development Award (IDeA) is to broaden the geographic distribution of NIH funding for biomedical and behavioral research. This is the second year in a row that NIH has proposed reducing funding for the IDeA program after Congress restored funding in the prior year. I question why the budget would reduce funding for the IDeA program whose purpose is to diversify biomedical research to all regions of the country when the budget requests new funding for new proposals to diversify the biomedical workforce. Why is NIH not supporting level funding for the IDeA program which is already a critical component of diversifying the biomedical research capacity?

Answer. At a time of difficult economic environment when many investigators throughout the Nation are struggling to compete for NIH funding, the allocation of funding for selected States to increase their competitiveness must be balanced with other NIH initiatives for promoting a more diverse biomedical workforce nationwide.

Question. The IDeA program is operating under a budget of $262.5 million for the remainder of fiscal year 2013. Dr. Collins, if your budget request of $226 million were agreed to, the IDeA program would issue no new Centers of Biomedical Research Excellence (COBRE) awards in fiscal year 2014 and cut the COBRE grants currently funded. Why would you propose funding reductions that require reducing existing awards to a current program whose goal is to increase diversity, while then proposing a new diversity initiative within the Common Fund?

Answer. The IDeA Program is a funding set-aside designed to build research capacity in selected States to the point where investigators in these States can compete for NIH funding. We have proposed returning the IDeA program appropriation to the level where it had been before the one-time spike in fiscal year 2012. The IDeA program is a congressionally mandated program envisioned as a long-term initiative for building biomedical research competitiveness of selected States while the Common Fund initiative is a limited term program designed to support student development from underrepresented groups.

Question. Given today's Federal budget constraints and drug companies' hesitation to pursue costly development of drugs that may have a low success rate, I believe programs like NCATS' Learning Collaborative is an innovative model to help address these issues. As we discussed in this hearing last year, the University of Kansas Cancer Center has engaged in a partnership with the National Center for Advancing Translational Sciences (NCATS) and the Leukemia & Lymphoma Society to repurpose auranofin, an arthritis drug, for use on a rare form of blood cancer. The Learning Collaborative has repurposed a drug from the shelf into a clinical trial in less than 2 years, and at one-sixth the cost of developing a new drug. Dr. Collins, could you talk about the progress the Learning Collaborative has made?

The success of this project appears clear—within 2 years, The Learning Collaborative has moved a compound to treat arthritis into a Phase IIa Clinical Trial to treat Chronic Lymphocytic Leukemia (CLL), a rare blood cancer. This project has not only shown promising results for those suffering from CLL, but the research

studying auranofin has also helped broaden our understanding of how the drug may work to fight other forms of cancer. As a result of this initiative, the University of Kansas was able to submit two additional investigational new drug applications to study auranofin's effects on other forms of cancer. Dr. Collins, do you expect this model to be replicated with other repurposing initiatives?

Answer. Parallel, independent studies conducted at The University of Kansas (KU) and University of Rochester demonstrated positive results when using auranofin to treat a rare, difficult to treat lymphoma called Mantle Cell Lymphoma. Investigators at both NCI cancer centers believe that auranofin acts synergistically with a class of anticancer agents called proteosome inhibitors (e.g., Velcade or bortezomib) to treat this cancer. Velcade is not very effective when given alone to treat this lymphoma. In a series of collaborative experiments with University of Kansas, NCATS obtained results supporting the use of Velcade with auranofin to treat this cancer. As a result, on March 15, 2013, KU investigators filed a second Investigational New Drug (IND) application with the Food and Drug Administration (FDA). In late April, FDA cleared researchers to proceed with a clinical proof-of-concept trial, studying auranofin alone and in combination with Velcade, in lymphoma patients. This trial will be conducted at the University of Rochester, University of Iowa, and University of Kansas NCI cancer centers.

Investigators at KU submitted a third IND on March 28, 2013, seeking clearance to study auranofin for the treatment of gastrointestinal stromal tumors (GIST). The cancer, GIST, afflicts approximately 4,000 U.S. patients. Auranofin is active, in the test tube, in treating GIST that is both sensitive and resistant to Gleevec. Very recently, investigators received clearance from the Food and Drug Administration (FDA) to proceed with this trial. The trial will be conducted at the University of Kansas Cancer Center and Children's Mercy Hospital in Kansas City, MO.

Auranofin was discovered as active against these cancer cells in screens of the NCATS Pharmaceutical Collection (NPC), a comprehensive collection and database of approved and investigational drugs. NCATS collaborates with investigators worldwide to identify other drugs in the NPC that can be repurposed for unmet medical needs.

Question. How will NCATS share the lessons learned in these types of collaborations so others in the field of translational research can benefit?

Answer. Sharing the lessons learned is the best way for NCATS to increase the impact of its programs. When the Center develops a strategy and demonstrates the value of that strategy, the dissemination and adoption of the strategy by other organizations in both the public and private sectors is how NCATS will amplify the impact of its investment. Such dissemination is accomplished via sharing of data and template agreements in public Web sites, peer-reviewed publications, and presentations to stakeholders. NCATS uses all of these strategies to disseminate lessons learned and communicate the value of our strategies. For example, NCATS collaborated with FasterCures, a center of the Milken Institute, to disseminate the collaborative lessons from The Learning Collaborative with KU and the Leukemia & Lymphoma Society (LLS) via webinars, and made the Research Collaboration Agreement (http://train.fastercures.org/pdf/tools/CollaborationAgreementNCATS 012412.pdf) and Memorandum of Understanding (http://train.fastercures.org/pdf/tools/RedactedMOU5June2012.pdf) public for others to use.

Question. Through Federal investment, the NIH has advanced our understanding of health for the last century. But the NIH provides more than medical discoveries, it creates and sustains jobs and produces measurable benefits to the American economy. Dr. Collins, at a time when global competitiveness in biomedical research is intensifying, and our global competitors are spending more funding to advance their own biomedical research efforts, can you discuss the ramifications of reducing the Federal investment in NIH?

Answer. Reducing the Federal investment in medical research has many ramifications. NIH is currently the largest funder of biomedical research in the world, and the work it supports and conducts leads to advances in the diagnosis, treatment, and prevention of disease. As you note, NIH research also has significant economic benefits and creates and sustains jobs in research and development. In "NIH's Role in Sustaining the U.S. Economy", United for Medical Research, an advocacy organization, calculated that the $23.7 billion spent by NIH extramurally in the U.S. in 2011 directly and indirectly supported 432,094 jobs. NIH funding also affects the size of the bioscience industry, according to the Milken Institute's 2012 report, "Estimating Long-Term Economic Returns of NIH Funding on Output in the Biosciences". The authors, representing an advocacy organization, argue that a $1 increase in NIH funding will increase the size (output) of the bioscience industry by at least $1.70 in that year.

NIH's current operating budget, post sequestration, of $29.15 billion is about 5 percent below last year's budget. In addition, in inflation-adjusted terms, the NIH budget has declined almost every year since 2003. Other countries are increasing their investment and threatening the U.S.'s leadership in the global life sciences industry. Between 1999 and 2009, Asia's share (including China, India, Japan, Malaysia, Singapore, South Korea, Taiwan, and Thailand) of worldwide R&D expenditures grew from 24 percent to 32 percent, while U.S. R&D expenditures declined from 38 percent to 31 percent. In addition, the European Commission has recently urged its member nations to increase substantially their investment in research, recommending budgets of 80 billion euros ($108 billion) in 2014–2020, a 40-percent increase over the previous seven year period.

As other countries continue to devote a larger share of their annual budgets to R&D, it will be essential for the U.S. to continue to invest in biomedical research, training, and infrastructure. These investments—critical components in the "engine of innovation"—will be needed to keep the U.S. in the position of worldwide leader. A sustained commitment to biomedical research, will allow NIH to keep up the pace of advancements in the treatment, diagnosis, and prevention of disease and in the improvement of the public health and for the U.S. to maintain its global lead in biomedical innovation.

Question. Dr. Collins, diseases such as Alzheimer's, cancer, diabetes, and heart disease affect millions of Americans and cost hundreds of billions of dollars to treat each year. We all know people who have been impacted by each of these diseases and how important the development of preventive measures, diagnostic tools, and new treatments are. Yet recent estimates for this year project that the NIH will fund the fewest number of new and competing research projects since 1998—the first year of the doubling of the NIH. What steps are being taken to ensure that we continue to make progress against these and other diseases?

Answer. NIH is operating at a program level of $29.15 billion in fiscal year 2013, a decrease of about 5 percent from fiscal year 2012. Despite this reduction, NIH remains committed to funding outstanding science and will continue to strive to find new, more effective ways to prevent, treat, and cure human diseases. NIH also remains committed to supporting the other critical elements of our mission, namely training and development of talented researchers and maintaining a technologically advanced scientific infrastructure.

The sequester is having real effects on our ability to support both new and competing research projects as well as non-competing continuation awards. Although NIH is likely to make fewer competing awards in fiscal year 2013, we will be trying to keep the average size of competing awards constant at fiscal year 2012 levels. Most non-competing continuation awards that have already been made in fiscal year 2013 were funded up to 10 percent less than the previously committed level. Although we may be able to make some adjustments during the year depending on the final level of each NIH Institutes and Centers' (ICs) appropriation, we will not be able to restore them to the previous level. Finally, new research infrastructure and core facilities are now ready for use, but without support for researchers who can take advantage of these resources, their productivity will not be fully realized.

NIH will be strategic in deploying its resources in fiscal year 2013 to achieve continued success in addressing the public health challenges of today and tomorrow including those you reference in your question. For example, to advance the progress of research on Alzheimer's disease, NIH will enable rapid sharing of data, disease models, and biological specimens, and it will promote the building of new multidisciplinary translational teams and create both physical and virtual sites where these teams can operate. NIH will also establish new public-private partnerships to speed drug development by repurposing abandoned compounds. NIH's Cancer Genome Atlas (TCGA), a joint effort of the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), is a publicly accessible database that is opening new avenues for the identification of useful biomarkers and the development of targeted therapies. Among efforts in diabetes research, NIH will work to translate the important findings of controlled clinical trials for diabetes prevention or treatment into approaches that are effective, affordable, safe, and sustainable in real world settings. For heart disease, NIH is funding studies of the cellular and molecular mechanisms underlying large conduit-artery stiffening in hypertension and the examination of the temporal relationship between arterial stiffening and the development of hypertension in animal models.

Using a priority setting process that strikes a dynamic balance between multiple factors, including ongoing and newly emerging public health needs, scientific opportunities, responses to unexpected scientific findings, and the need to sustain longer-range workforce and infrastructure development, NIH is able to support all of our mission areas. This process and the continuous monitoring and evaluation of re-

search portfolios help ensure an ever-increasing understanding of basic biological functioning and the application of that understanding to the amelioration of disease burden. Nevertheless, decreased funding will limit NIH's ability to fund all of the most promising scientific ideas and affect the pace of the advances we generate in the treatment, diagnosis, and prevention of disease and in the improvement of the public health.

Question. The fiscal year 2014 budget request proposes a multi-agency reorganization of science, technology, engineering, and mathematics (STEM) education, which includes nine consolidations of NIH-related STEM programs to other agencies. What is NIH's plan with respect to the STEM education proposal?

Answer. The fiscal year 2014 President's budget proposes to consolidate a number of science education programs under the Department of Education, the National Science Foundation, and the Smithsonian Institution. NIH staff have participated in preliminary transition planning discussions with representatives in those three agencies, and we are preparing for phase out of those programs. While K–12 science education is important, it is not a core NIH function given our focus on training the scientific workforce at the undergraduate, graduate, and doctoral levels.

Question. NCATS' Learning Collaborative has incorporated resources from the NIH, a State university, and a nonprofit advocacy organization to develop new therapeutics for blood cancers. It is my understanding that this public-private collaboration was made easier by using a Collaboration Research and Development Agreement (CRADA). Do you expect NCATS to continue to use CRADAs in future collaborations?

Answer. A Collaboration Research and Development Agreement (CRADA) is a useful tool for formalizing collaborations between intramural NIH scientists and university and industry scientists, and NCATS is utilizing this agreement type for many of its collaborations with for-profit and non-profit organizations. NCATS anticipates continued usage of the CRADA mechanism, due to the collaborative nature of many of NCATS programs.

Question. Do any changes need to be made to allow for the NIH to better leverage the benefits of CRADAs?

Answer. While there are various mechanisms that support collaborations between companies and NIH intramural scientists, the CRADA is the only mechanism that permits the NIH to offer an upfront option to companies to license inventions that may be made within the scope of the collaboration agreement, and it also permits the collaborating company to provide funds to the NIH in support of the research. Over the last few years, the number of CRADA collaborations has steadily increased with new inventions being developed as a result of these critical scientific relationships. Currently, NIH is developing an online system that will tailor the CRADA terms to the specific needs of the collaboration and streamline the negotiation and implementation processes. As NCATS and other ICs explore innovative collaborative relationships with the private sector, NIH is flexible in adapting CRADAs to meet those programmatic needs.

QUESTIONS SUBMITTED BY SENATOR RICHARD C. SHELBY

Question. The budget proposes a government-wide realignment of Federal science, technology, engineering, and mathematics (STEM) education programs. Dr. Collins, do you support the Office of Management and Budget's proposal to move nine of the National Institutes of Health's (NIH) STEM education programs to other agencies?

Answer. The NIH supports the proposal in the fiscal year 2014 President's budget to consolidate K–12 science education programs under the Department of Education, the National Science Foundation, and the Smithsonian Institutions. NIH staff are participating in initial transition planning discussions with representatives in those three agencies, and we are considering phase out of those programs. While K–12 science education is important, it is not a core NIH function given our focus on training the scientific workforce at the graduate and doctoral levels.

Question. Without Congressional approval, NIH could still move forward to consolidate STEM education programs within NIH. Do you think you will move in that direction should Congress not act on the government-wide realignment?

Answer. The NIH is supportive of efforts to improve coordination of Federal science education programs consistent with the President's desire to take action to improve student outcomes. The NIH is reviewing its K–12 science education programs in light of reorganization and consolidation of STEM education proposed in the fiscal year 2014 President's budget, but cannot speculate on a scenario where Congress does not act on the government-wide proposal.

Question. Dr. Collins, the budget request proposes a new diversity program in the Common Fund called NIH Building Infrastructure Leading to Diversity (BUILD). The budget justification states that the program would support initiatives to strengthen the infrastructure of "comparatively under-resourced institutions."

What are the eligibility criteria for this proposal?

Answer. NIH intends for BUILD awards to involve partnerships from multiple types of institutions, but only those that are referred to as Primary Institutions would submit applications. Primary Institutions, the applicant organization, are intended to be those that have the primary responsibility for implementation of the project and for management of the award. NIH intends for Primary Institutions to be baccalaureate-granting colleges/universities that receive less than $7.5 million (total costs) in NIH research project grants (RPG) (average of fiscal years 2010–2012) and have a pool of undergraduate students, at least 25 percent of whom are supported by Pell grants. The BUILD Primary Institution eligibility criteria are intended to target funds to relatively under-resourced institutions (less than $7.5 million in NIH RPG funding) with a demonstrated commitment to students from diverse backgrounds that have been historically underrepresented in the biomedical research workforce. The intended requirement that BUILD institutions have a substantial pool of students from disadvantaged backgrounds (at least 25 percent must be Pell grant recipients) is based on the recognition that (1) many students from economically disadvantaged backgrounds are underrepresented in the NIH workforce in the fields of biomedical, behavioral, and clinical research, and (2) institutional commitment to these students often comes at the expense of investments in research infrastructure.

Primary Institutions will be encouraged, but not required, to develop appropriate partnerships in order to optimally position themselves to provide a rigorous environment for research training. Partnerships involving a Primary Institution and one or more of the following institution types are encouraged:

Pipeline Partner Institutions are intended to be 2- or 4-year undergraduate institutions with students that will enrich and expand the pool of students eligible for BUILD scholarships. Research Partner Institutions are intended to be research intensive institutions with committed investigators able to serve as effective research mentors for BUILD scholars. Research partnerships are intended to expand education and research opportunities available to BUILD scholars, work with Primary Institutions to develop innovative curricula, and provide sabbatical opportunities to faculty from Primary Institutions. Academic institutions, government institutions, industry, and nonprofit research institutions may all be considered as potential Research Partners. Graduate/Medical Partner Institutions are intended to be medical, dental, or graduate research institutions with no undergraduate program but with a pool of doctoral-level students engaged in research and/or planning a research career, and less than $7.5 million (total costs) through research project grants (average of fiscal years 2010–2012). Primary Institutions and Graduate/Medical Partner Institutions are intended to work collaboratively to provide joint programs for both undergraduate and graduate students.

In addition to the BUILD initiative, the NIH Common Fund's "Increasing the Diversity of the NIH-Funded Workforce" program includes two other initiatives: the National Research Mentoring Network (NRMN) and the Coordination and Evaluation Center (CEC). The NRMN is intended to facilitate the development of robust mentoring relationships by coordinating nationwide pairings of scientific leaders and early career scientists (undergraduate students through junior faculty members) who may benefit from additional mentoring, including but not limited to individuals from underrepresented backgrounds. The CEC is intended to serve as a centralized hub to enable the integration of BUILD and NRMN with existing programs, assessing the impact of the BUILD and NRMN initiatives from the earliest stages of implementation to provide early indications whether the novel approaches implemented by BUILD and NRMN awardees are having a meaningful effect. NIH intends for both the NRMN and CEC to be open to any institution within the United States, including academic institutions, nonprofits, and professional organizations.

Question. How many institutions do you propose funding with fiscal year 2014 funds?

Answer. In fiscal year 2014, we expect to support approximately ten Primary Institutions within BUILD, each of which will be encouraged to form partnerships with other institutions as appropriate. In addition, we expect to support one institution within NRMN, and one institution within CEC. The number of institutions supported will be contingent upon availability of funds and receipt of a sufficient number of meritorious applications.

Question. How much do you expect the awards to be?

Answer. Details of the anticipated budgets for BUILD, NRMN, and CEC will be provided in the Funding Opportunity Announcements for these initiatives, which are expected to be released in the fall of 2013. As described in a presentation to the NIH Advisory Committee to the Director (http://acd.od.nih.gov/Diversity-in-the-Biomedical-Workforce-Implementation-Plan.pdf), the entire "Increasing Diversity of the NIH-Funded Workforce Program" budget is planned to average approximately $50 million per year. The majority of these funds are intended to go towards the BUILD initiative.

All anticipated award budgets are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

Question. Could you please provide additional details beyond those provided in the Funding Opportunity Announcement, related to the expected collaboration between the Primary, Pipeline, Research and Graduate/Medical Partner institutions? (OD/Common Fund)

Answer. NIH intends for BUILD Primary Institutions to be encouraged, but not required, to partner with Pipeline Partners, Research Partners, and/or Graduate/Medical Partner Institutions. The intent of encouraging these partnerships is to provide the best research training environment for students involved in the BUILD program. Partnerships with Research Partners would allow students from under-resourced institutions to participate in robust research experiences that are unavailable at their home institutions. Participation in mentored research experiences is a critical factor in determining whether undergraduate students choose to pursue a research career; therefore, engaging students from underrepresented backgrounds in meaningful research experiences is anticipated to have a major impact on the diversity of the biomedical research workforce. Primary Institutions and Research Partners are intended to also work together to develop novel curricula, and faculty from Primary Institutions are intended to have the opportunity to pursue sabbatical activities at Research Partner Institutions. Partnering with Pipeline Partner Institutions will enrich the pool of students eligible to participate in the BUILD programs, so that students at 2- or 4-year colleges (such as community colleges) can benefit from research training experiences not available at their home institutions. Similarly, partnerships with Graduate/Medical Partner Institutions are intended to also expand the pool of BUILD-eligible scholars by providing additional research experiences to doctoral-level students at these institutions. NIH intends for Graduate/Medical Partner Institutions to include Historically Black Medical/Graduate Schools, which have a rich history of training students from underrepresented backgrounds and have a robust pool of students who may benefit from BUILD activities.

Question. Dr. Collins, you stated at the hearing that while the Administration has proposed an overall goal of mapping the human brain, there are no specific scientific details or timeline you can put forward at this time. While I understand that you expect fiscal year 2014 to be a scientific planning year, it is critical that the Appropriations Committee has a full understanding of the goals and timeframe of this project before funding is appropriated. Therefore, can you please provide the subcommittee with the following information:

The BRAIN Initiative has no clearly defined goals or endpoint. When do you expect to have a scientific framework in place to answer these critical questions?

Answer. NIH is undertaking a rigorous scientific planning process to determine the scientific aims of the NIH component of the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which is anticipated to include a plan for timetables and milestones. As part of this process, members will consult the scientific community, patient advocates, and the general public to ensure that this plan is informed by a broad and inclusive input. Final recommendations are anticipated in the summer of 2014, at which time the NIH will be able to comment on the scientific framework.

Question. How long do you estimate mapping the human brain will take?

Answer. The goal of the BRAIN Initiative is not actually to map the brain, per se, but rather to accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought. These technologies will open new doors to explore how the brain records, processes, uses, stores, and retrieves vast quantities of information, and shed light on the complex links between brain function and behavior. The group advising the NIH on the scientific framework for the BRAIN Initiative has been asked to articulate the short, mid, and long term objectives required for achieving these aims.

Question. What goals do you expect to accomplish in 1, 3, and 5 years?

Answer. It is premature to speculate on the accomplishments in the absence of a strategic plan outlining the scientific goals of the Initiative.

Question. Do you expect the Department of Defense and the National Science Foundation to continue to financially support this project for the duration?

Answer. NIH cannot comment on the financial commitments of the other agencies. However, given the different perspectives and strengths of each agency, NIH sees much benefit in having other agencies involved.

Question. What specific role will each Federal agency contribute to this project?

Answer. In general, NIH will develop new tools, training opportunities, and other resources. The Defense Advanced Research Projects Agency (DARPA) intends to explore applications—such as a new generation of information processing systems and restoration mechanisms—that dramatically improve the way we diagnose and treat soldiers suffering from post-traumatic stress, brain injury, and memory loss. The National Science Foundation (NSF) has expressed a commitment to supporting research that spans physical, biological, social, and behavioral sciences. Moving forward the agencies will work in close collaboration to ensure that their efforts are complementary and leverage the unique missions of each; ultimately catalyzing an interdisciplinary effort of unprecedented scope.

Question. It has been reported that the first several years of the program will emphasize the development of technologies. However, this approach has been criticized and some neuroscientists have said that money would be better spent by first figuring out what needs to be measured and then determining the best means to measure them. How do you respond to this critique?

Answer. The group advising the NIH on the scientific framework for the BRAIN Initiative has been asked to review the neuroscience landscape in order to determine the opportunities, challenges, and impediments in neuroscience research. It is precisely through this analysis that they will indeed assess what needs to be measured or what is missing in order to focus the investment in promising areas of research.

Question. The European Union (EU) has a similar initiative called the Human Brain Project. How is the BRAIN Initiative different than the EU program?

Answer. The EU's Human Brain Project and the BRAIN Initiative share the broad goal of advancing the understanding of the brain and its diseases. They also both recognize that technological opportunities are emerging to accelerate progress toward that goal. However, the two initiatives differ in their emphasis. The European Project emphasizes the development of informatics and computer infrastructure to systematically integrate all available data into unifying models of the brain. The BRAIN Initiative will focus on the development of tools that will transform our ability to gather new data, heretofore impossible to acquire, that will advance understanding of how millions of brain cells work together in circuits that enable us to think, act, and sense the world. That said, it is important to emphasize that the EU Project is new, multi-faceted, and will develop over time, and the BRAIN Initiative is in its early formative stages. As the BRAIN Initiative Working Group develops plans for the BRAIN Initiative, including how to analyze and disseminate the data it generates, the group is building bridges to the EU Project and to other projects outside of the U.S. government to take advantage of all possible opportunities for synergy.

Question. Do you expect collaboration with the EU on the ultimate goal of mapping the brain in its entirety?

Answer. As part of the working group's charge, they have been asked to identify areas in which collaboration with others (i.e. foundations, industry, other agencies) would result in either complementary activities or the leveraging of efforts. EU efforts will be considered in this analysis.

QUESTIONS SUBMITTED BY SENATOR LAMAR ALEXANDER

Question. You testified that sequestration caused the National Institutes of Health (NIH) to cut 700 extramural grants. Was intramural grant funding similarly affected? If so, are extramural and intramural on the same "playing field?" It is my understanding that extramural grants must go through a competitive peer-review process, which might not be the case for intramural grants.

Answer. The NIH Intramural Research Program has been subjected to similar cuts due to sequestration as extramural grants. The cuts in intramural and extramural research similarly affect hiring, purchase of equipment and supplies, scientific travel, etc. In addition, some clinical trials conducted through extramural research are being delayed, and reductions in intramural research will cause approximately 750 fewer new patients to be admitted to study protocols at the NIH Clinical Center. All NIH intramural principal investigators undergo rigorous peer review at least once every 4 years by outside scientific experts whose advice affects the re-

sources allocated to them. These experts are members of the scientific community who receive extramural grants, and they are thus in a position to compare the intramural research with research that is funded by extramural grants. Intramural scientists do not, however, receive actual grants but rather compete for and receive internal funding and resources for scientific programs and projects, thus making direct comparisons in numbers of grants difficult.

Question. According to your testimony, an average of 15–16 percent of grant applications to NIH submitted actually receive funding.

Are all grant applications submitted included as part of this statistic or do are only those grants that pass a minimal standard initial screening process included?

Answer. The National Institutes of Health (NIH) reports success rate statistics http://report.nih.gov/NIHDatabook/Charts/Default.aspx?showm=Y&chartId=124&catId=13 on the RePORT Web sites for various grant application types. The success rate in fiscal year 2012 for research project grants was 18 percent, and it is projected that the success rate for fiscal year 2013 will decline. Decreases in the Success rates are tied to availability of funding and the number of applications received, thus the overall growth in the number of applications reduces the success rate.

The success rate describes the percentage of grant applications accepted for peer-review that were subsequently funded. A small fraction of applications submitted to NIH are not accepted for review for various reasons, and thus, are not included in the success rate calculation. Examples would include if the applicant institution is ineligible for the funding program for which it has applied, or does not have active registrations in the United States System for Award Management and/or NIH's Electronic Research Administration (eRA) Commons. Some applications are not accepted because they are missing required information or violate application formatting requirements. Finally, a small number of applications are submitted that describe research projects that are virtually identical to applications previously reviewed, or do not fall within NIH's mission, and are not accepted for review.

Question. Of the total number of grant application submitted, what percentage are such that, even with unlimited funding, would not be worthy of funding? For what reasons would they be excluded?

Answer. Most grant applications submitted to the NIH are from recognized scientific experts and many are worthy of funding. Nevertheless, it is desirable to maintain a highly competitive process to identify the best science to support with the resources available. As part of the initial peer review process, reviewers have the ability to identify a particular application as Not Recommended for Further Consideration, if it lacks significant and substantial merit; presents serious ethical problems in the protection of human subjects from research risks; or presents serious ethical problems in the use of vertebrate animals, biohazards, and/or select agents. Applications designated as NRFC do not proceed to the second level of peer review (National Advisory Council/Board) because they cannot be funded. This is a very rare event, and all other applications are considered to have been recommended by the initial review group as eligible for funding. The Institutes and Centers typically regard applications that have been assigned Overall Impact Scores better than the 33 percentile to be worthy of consideration for funding. However, each NIH Institute and Center (IC) may fund applications that do not meet this threshold, if they can establish high program relevance. Indeed, the success rate for Research Project grants reached 32 percent during 1999 to 2001; however, the high success rate is tied to the relatively low number of applications received. For example, in 1999, NIH received about 26,000 applications, compared to the over 50,000 received in 2012.

Question. How is NIH working with private foundations regarding young investigator awards? What percent of young investigator awards are being funded by NIH?

Answer. NIH identifies New Investigators as those who have not previously competed successfully as the Project Director or Principal Investigator for a substantial NIH independent research award, e.g., an investigator-initiated R01 Equivalent Grant (R01, DP2 or R37). It is the goal of NIH to support New Investigators on new, R01 equivalent awards at success rates comparable to those of established investigators submitting new or Type 1 applications. In fiscal year 2012, NIH awarded 1,286 competing R01 equivalent grants to New Investigators, for a success rate of 13 percent. There were 2,429 comparable awards made to established investigators, for a success rate of 15 percent.

NIH has a novel program for intramural scientists that is coordinated collaboratively with the Lasker Foundation. The Lasker Clinical Research Scholars Program supports a small number of exceptional clinical researchers in the early stages of their careers to promote their development as independent investigators. Scholars receive 5 to 7 years of support as an independent principal investigator in the NIH Intramural Research Program, followed by the competitive opportunity for addi-

tional years of financial support, either at the NIH or at an extramural research institution.

Question. The National Cancer Institute (NCI) assembled a list of 24 questions that should engage scientific community in debate and further advancements in cancer research. What is the timeline for measurable outcomes for the NCI Provocative Questions program?

Answer. The Provocative Questions Initiative (PQI) has lofty goals but it is less than 2 years old, so the outcomes that can be measured now are largely procedural and subjective. The PQI was designed to engage the scientific community in efforts to identify important and often long-standing questions in cancer research—e.g., how obesity contributes to the development of cancers or why some cancers respond to specific drugs when others do not—and to address them experimentally, using new methods and new information. Part of the motivation was to encourage the research community to take risks and address important problems, even in this time of limited funding and low success rates. The ultimately desired outcomes of the PQI will be answers to at least some of the questions and applications of the answers to the ways in which cancers are prevented, diagnosed, and treated. But such outcomes cannot be expected for at least 5 to 10 years.

Other aspects of the PQI—its attractions for the cancer research community and its capacity to generate interest and exciting ideas—can be measured, however, even at this early stage. For instance, the PQI was designed to stir imaginative, interdisciplinary thinking by asking working scientists, rather than NCI program directors, to develop the Provocative Questions. As measures of the enthusiasm generated by this project, we have kept track of the many PQI workshops that the NCI has conducted throughout the country, bringing scientists from different disciplines together to propose and discuss questions; and we have observed the heavy traffic on our PQI Web site, where questions are posted and debated. When we selected twenty-four questions to be addressed in the first round of competition for grants, we received over 750 applications, indicating a high level of interest and we funded slightly more than fifty of the best applications. The NCI is currently evaluating a second set of applications received in response to Provocative Questions.

Question. Please address any overlap between the NIH Common Fund and the NIH National Center for Advancing Translational Sciences. How are these two areas coordinating efforts?

Answer. By design, the Common Fund is not separate from the ICs. Scientific oversight for each Common Fund Program is provided by two or three IC Directors who serve as co-chairs. Requests for applications (RFAs) are issued from the IC of one of the co-chairs and day-to-day and long-term program oversight is provided by staff from the co-chairs' ICs. In addition, each program has a trans-IC Working Group composed of program staff from as many ICs as are interested in participating. Successful coordination of this distributed management model is the responsibility of the Office of Strategic Coordination in the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), NIH Office of the Director (OD). There are several programs within the National Center for Advancing Translational Sciences (NCATS) that originated from, and are currently being funded, either fully or partially, by the Common Fund. These include the Bridging Interventional Development Gaps (BrIDGs) program; the NIH Chemical Genomics Center (NCGC), which is part of the Common Fund's Molecular Libraries and Imaging program; the Tissue Chips for Drug Screening program and the Discovering New Therapeutic Uses for Existing Molecules program, which are both part of the Common Fund's Regulatory Science program; and the Extracellular RNA Communication program. For all of these initiatives, there is ongoing coordination between NCATS and Common Fund staff, with guidance from trans-NIH working groups. Complementarity between the Common Fund and NCATS in how these programs are currently conceptualized, managed, and led on behalf of the trans-NIH community.

The fiscal year 2014 President's budget requests additional funding for NCATS so that support for several of these programs can be shifted from the Common Fund to NCATS.

Question. One of the newest entities within the NIH is the NCATS. Could you provide the committee with an update on some of NCATS' current activities and planned expenditures in fiscal year 2014? I am especially interested in the Clinical Translational Science Awards (CTSAs) program, which I believe the Institutes of Medicine is currently reviewing at NIH's request. Vanderbilt University in Nashville is the coordinating center for the 60 research institutions linked by this program, which supports local and national research communities to improve the quality and efficiency of all phases of translational research. Going forward, how do you envision building on the work of CTSA recipients to complement other NIH initia-

tives in translational science? How do you see the CTSA program working with Foundations, patient advocacy groups and industry?

Answer. To bring the benefits of science more quickly into patient care, the NCATS was formed with the mission to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. NCATS' mission includes strengthening the entire spectrum of translational research—defined broadly to include the early steps necessary to develop new therapeutics, devices and diagnostics from basic discoveries, the steps necessary to establish real world efficacy, and the research needed to improve the practical implementation and dissemination of improved approaches to care.

NCATS will utilize a number of programs to accomplish its mission across this translational spectrum. Extending the success of the CTSA program in transforming the local and regional environment for translational research to, in turn, transform the national environment for translation will be a central component. In order to accomplish this transformation across a broad spectrum of diseases and conditions, NCATS will focus on collaboration in and across all of its programs. Key partners will include, but are not limited to, other NIH Institutes, Federal agencies, patient advocacy groups, professional societies, foundations, healthcare systems, and a wide range of commercial entities. NCATS will leverage and build on existing relationships with many foundations, patient advocacy groups and industry, as collaborators, advisors, committee members and program partners.

NCATS engaged the Institute of Medicine (IOM) to review the CTSA program and provide recommendations for any changes needed in the program. The report was released at the end of June and NCATS is reviewing the recommendations of this group as we work to evolve the CTSA program within NCATS.

QUESTIONS SUBMITTED BY SENATOR MARK KIRK

Question. BrainGate is a promising technology. How does the National Institutes of Health (NIH) plan to integrate promising technologies like BrainGate—and other existing stroke research priorities—with the proposed Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative?

Answer. The BrainGate neural interface system is a promising type of brain-computer interface intended to put prosthetic arms and other assistive technologies under the control of people who are disabled because of a stroke or other neurological disorder. Using BrainGate in a controlled laboratory setting, a paralyzed woman was able to move a robotic arm and take a sip of coffee on her own for the first time since she had been paralyzed more than 14 years earlier. BrainGate consists of sensors implanted in the brain that monitor signals from nerve cells in a brain area that controls movement, and computer software and hardware that translate these signals into digital commands for assistive devices. A clinical trial, funded in part by the NIH, is evaluating the safety and feasibility of this device.

The BRAIN initiative will advance the prospects for more effective brain computer interface devices in two ways. First, BRAIN will develop tools that will transform researchers' capabilities to monitor larger numbers of brain cells, in a less invasive manner, more stably over time. This addresses major limitations of the current generation of brain computer interfaces, which monitor relatively few cells and rely upon invasive electrodes that often do not maintain a stable signal over time. Second, with the tools from BRAIN in hand, researchers will learn to better understand the "neural code" by which brain circuits control movement and perceive the environment. This will enable the design of devices that interface with brain circuits more effectively to provide precise and natural movement control and sensory feedback.

The potential for extraordinary long-term benefits of the BRAIN Initiative is tantalizing, with transformative technologies for recording nerve cells now in use or on the horizon, including those that rely on optical signals. However, these technologies are currently not suitable for use in humans, and laboratory research in animals, including those with much simpler brains, will initially be a focus of BRAIN. NIH is continuing to support the near-term development of brain computer interfaces, such as BrainGate, as we also invest through the BRAIN Initiative in research that will revolutionize the understanding of the brain and its disorders in the future.

Question. Rehabilitation research is cross-cutting within NIH. What is NIH doing to prevent duplication in research?

Answer. NIH's rehabilitation research efforts include a range of studies from developing next generation prostheses and assistive devices, to optimizing physical,

cognitive, and combination drug therapies. A number of NIH Institutes and Centers (ICs) support extensive research related to medical rehabilitation.

Although multiple ICs are involved, they proactively work to coordinate their activities and prevent duplication of efforts. For example, the Eunice Kennedy Shriver National Institute of Child Health and Human Development's National Center for Medical Rehabilitation Research (NCMRR) supports research needed to enhance the health, productivity, independence, and quality-of-life of people with disabilities. The Center's role includes coordination of medical rehabilitation research, and promoting research specific to the health related problems of people with disabilities in order to capitalize on advances occurring in the biological, behavioral, and engineering sciences. The Center's work has been aided by a blue ribbon panel formed in 2011 to focus on medical rehabilitation research at NIH. The panel conducted an analysis of rehabilitation science activities within the NCMRR and across the NIH to identify the most promising research opportunities which was reported to the National Advisory Child Health and Human Development Council.

In addition, NIH has an established record of identifying scientific areas of potential overlap and developing trans-NIH programs, activities, and policies to optimize the strengths and expertise within each of the ICs and to ensure the complementarity of their programs and activities. The Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) in the Office of the Director works closely with the NIH Institutes and Centers (ICs) to plan and coordinate trans-NIH research cross-cutting activities. As part of this process, DPCPSI will work with all relevant ICs to conduct a portfolio analysis designed to identify scientific gaps and areas of sufficient investment.

DPCPSI's Office of Portfolio Analysis provides consultation and training to NIH program staff in the use of portfolio analysis tools that allow IC staff to identify gaps in specific research portfolios and areas that are adequately funded across ICs. Such evaluation tools provide data to enhance prioritization efforts of current and emerging areas of research, and also prevent unnecessary overlaps and duplication of effort.

Administrative processes are also in place to monitor for scientific overlaps in funding opportunity announcements (FOAs) and in grant applications. At the FOA stage, the new Guide Publishing System allows ICs to review of funding opportunity announcements prior to publication. When grant applications are received, duplicative proposals can be identified at the receipt and referral stage and at the peer review stage. After review, meritorious applications are checked for other sources of support, including all existing and pending financial resources, whether Federal, non-Federal, commercial or organizational, to determine whether there may be budgetary, scientific, or commitment overlap. This step is key to identifying and eliminating duplicative proposals.

QUESTIONS SUBMITTED TO DR. STORY C. LANDIS

QUESTION SUBMITTED BY SENATOR TOM HARKIN

Question. Dr. Landis, when you add up the contributions from your private sector partners—the Allen Institute for Brain Science (at least $60 million/year), the Howard Hughes Medical Institute (at least $30 million/year), and others—they're planning to contribute approximately the same amount or more as the President is requesting. Do you expect the same situation in future years of the initiative?

Answer. Each partner has a long-standing commitment to neuroscience research and we do not anticipate that their contributions to the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative will be a one-time event. However, details of the initiative are still under development as part of a rigorous scientific planning process, for which final recommendations are anticipated in the summer of 2014. This plan will be widely shared with both the public and with our BRAIN Initiative partners.

QUESTIONS SUBMITTED TO DR. RICHARD J. HODES

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

Question. Dr. Hodes, the RAND Corporation recently released a report that found that the cost of caring for all Americans with dementia in 2010 was between $157 billion and $215 billion. By 2030, the number of Americans with dementia is expected to more than double. A few statistics:

—Medicaid payments alone are 9 times higher for those with Alzheimer's compared to those without the disease.
—64 percent of Medicare beneficiaries in nursing homes over 65 years old have Alzheimer's disease or other dementia and Medicare pays approximately $11 billion a year for their care.
—Each dementia case costs between $41,000–$56,000 a year.

We know that these numbers will only increase as our population ages. I support the National Institutes of Health (NIH) for many reasons—the impact to health being paramount. But another key component of my support is that I believe if we can find effective treatments for diseases like Alzheimer's and dementia, we can not only extend quality of life for patients, but reduce the cost of caring for these patients in years to come. Could you discuss some of the research projects the National Institute on Aging will fund if this proposal is approved and the impact these projects could have on our Nation's healthcare costs?

Answer. Pending availability of funds, the ongoing Alzheimer's disease (AD) research supported by the National Institute on Aging (NIA) will continue in 2014, along with several recently launched efforts made possible with increased funding. These include:

—Whole genome sequencing to identify new genetic variants that either increase risk (risk factors) or reduce risk (protective factors) for AD (in collaboration with the National Human Genome Research Institute).
—A treatment trial to test the effectiveness of intranasal insulin in individuals with mild cognitive impairment or mild Alzheimer's dementia on cognition and daily functioning.
—A 5-year prevention trial to test the ability of an antibody called crenezumab to bind to and clear away abnormal amounts of amyloid protein in the brain and prevent cognitive decline in people with early-onset AD.
—Research to be funded in fiscal year 2013 and fiscal year 2014 under four 2012 Funding Opportunity Announcements supporting drug discovery, development, and preclinical and clinical testing for the treatment and prevention of Alzheimer's disease and dementia.

In addition, recent scientific advancement suggests that some new activities may be feasible. If so, we anticipate new activities in the following areas in fiscal year 2014:

—*Additional Drug Development and Testing*.—This will include support for drug repurposing and combination therapy, phase 2 (proof of concept) drug trials for agents against currently known therapeutic targets, and studies of possible agents against not-yet-known therapeutic targets for AD.
—*Non-Pharmacological Intervention Development*.—We will focus on advancing non-pharmacological interventions for the cognitive and behavioral symptoms of AD and the design of approaches that combine pharmacological and non-pharmacological treatments.
—*Biomarkers of Disease Progression to Measure the Effects of Potential Treatments*.—We will test imaging and fluid biomarkers for the assessment of disease-related pathology, work to develop and validate sensitive measures to detect and track the earliest clinical changes of AD, and develop and test methods for the standardization of neuroimaging procedures and data collection.

The issue of the impact of this research on healthcare costs is highly complex. Alzheimer's disease treatment and care place an enormous financial and economic burden on patients, their families, and the healthcare system, as illustrated by the NIA-supported study from the Rand Foundation noting that the costs of caring for people with dementia in the United States in 2010 were between $159 billion and $215 billion, and could double by 2040. Estimates of cost savings resulting from an effective therapy need to account for a number of factors, including the cost of the therapy itself, which could be significant, or savings offset by other costs of providing care to those surviving patients.

Question. Many diseases are increasingly common with older age. What efforts is NIH making to understand the aging process and its relationship to these diseases?

Answer. Age is a primary risk factor for many disabling diseases and conditions, and NIH supports a robust program of research aimed at understanding the relationship between aging and disease and disability. Ongoing initiatives include:

—*NIH Geroscience Interest Group*.—The NIH Geroscience Interest Group (GSIG) was established in 2012 to accelerate and coordinate efforts to promote further discoveries on the common risks and mechanisms behind age-related diseases and conditions by developing a framework that includes multiple NIH Institutes. By pooling resources and expertise, the GSIG identifies major cross-cutting areas of research and proposes coordinated approaches to identify hurdles and envision solutions. In September 2012, the GSIG sponsored a workshop on

inflammation and age-related diseases, and this activity has led to a Funding Opportunity Announcement on the subject, co-sponsored by several NIH Institutes. As a way of gaining further input from the research community, a larger-scale workshop titled "Geroscience: Foundations for Delaying Chronic Disease and Increasing Healthspan" is planned for fall 2013. This two and a half day forum will bring together 53 leaders from the fields of aging and major chronic diseases.

—*Nathan Shock Centers on the Basic Biology of Aging*.—NIH supports five Nathan Shock Centers on the Basic Biology of Aging. These Centers provide leadership in the pursuit of basic research into the biology of aging through a Research Development Core which administers small start-up funds locally, and organizes national annual meetings to highlight specific areas of research. In addition, each Nathan Shock Center has several specialized cores that provide services to other investigators. The cores are different in each Center, depending on the strengths of each Institution. Funding for the Nathan Shock Centers is slated for renewal in fiscal year 2015.

—*Interventions Testing Program (ITP)*.—This ongoing program, which began in 2003, supports the testing of compounds with the potential to extend the lifespan and delay disease and dysfunction in a mouse model of aging. A number of interventions, including foods, diets, drugs, and hormones, are tested through the ITP, and some compounds, such as rapamycin, have been found to increase not only lifespan, but health as well. Further research is ongoing, and a parallel program has been established to test interventions in the worm model "Caenorhabditis elegans".

Question. How might this understanding allow better treatment or prevention?

Answer. A better understanding of the basic biochemical, genetic, and physiological mechanisms underlying the process of aging and age-related changes will provide insight as to how these changes become risk factors for (or accompany) age-related disease and disability. This, in turn, will suggest interventions that may increase both lifespan and health span in older adults.

An example of basic discovery that may suggest pathways for prevention of disease and disability is the exciting research being conducted around cellular senescence and aging. Senescent cells no longer divide but still function within the organism and until recently scientists believed that they were very rare in living organisms and would not play an active role in aging. However, NIH-supported investigators recently found that high levels of senescent cells actually do accumulate in many tissues in aged mice, and may be an early marker of cancer—in fact, the earliest marker of cancer described to date. In a separate study, removal of senescent cells in mice delayed the onset of disease-related changes in skeletal muscle, fat, and eye tissues. In addition, removing senescent cells later in the life of the mice slowed the progression of already established age-related disorders. While research on cell cultures has long suggested that senescent cells have a role in aging, the nature of this connection in live animals was less clear. The new finding suggests that cell senescence may be a fundamental mechanism that drives aging, and provides a clear target for interventions to prevent age-related damage to cells and tissues.

Question. Dr. Hodes, as a nation, we invest a significant amount of funding towards healthcare. What is the NIA doing—and what should the NIA do—to expand and translate research on prevention and wellness for our rapidly aging population?

Answer. Recent NIA-supported studies conducted by the National Academy of Sciences have shown that although the United States spends more on healthcare than any other nation, Americans are in poorer health and live shorter lives than people in many other high-income countries. This health disadvantage exists across the lifespan, from birth to age 75. Many of the reasons behind these disparities appear to be behavioral and social—for example, Americans are more likely to engage in certain unhealthy behaviors, such as heavy caloric intake and behaviors that increase the risk of fatal injuries. However, even Americans who have health insurance, college educations, and higher incomes who adopt healthy behaviors appear to be sicker than their peers in other wealthy nations. The reasons for these disparities remain unclear. NIA continues to support research to determine the factors that contribute to premature mortality and lower disability adjusted life years in the United States, as well as the prospects for modifying such risk factors.

In addition, NIA supports a number of studies of interventions to prevent disease and disability. For example, the ongoing Lifestyle Interventions and Independence for Elders (LIFE) Study, a major clinical trial comparing the effects of a moderate-intensity physical activity program to a health education program on prevention of mobility loss disability in older Americans, began in 2010. In addition, NIA supports a number of studies exploring the effects of exercise and physical activity on every-

thing from mobility to mood and cognition. NIA also supports studies of a variety of interventions for health conditions common to old age. Ongoing studies include: the ASPirin in Reducing Events in the Elderly (ASPREE) trial, designed to determine whether the benefits of aspirin outweigh the risks in people over age 70; testosterone supplementation to delay or prevent frailty in older men; and an array of interventions for menopausal symptoms.

Translation of research findings related to healthy aging is an important priority for the NIA. For example, we support 13 Edward R. Roybal Centers for Translational Research in the Behavioral and Social Sciences of Aging, which stimulate broadly based multidisciplinary research that improves the health, wellbeing, and productivity of older adults. The Roybal Centers focus on diverse topics including health and mobility, disease and pain management, and decisionmaking and behavior change.

NIA also supports a successful program of communication and health education for older adults, their caregivers, and healthcare providers. For example, recognizing the value of exercise, the NIA partnered with the U.S. Surgeon General to launch its nationwide "Go4Life" campaign. This program is designed to motivate older Americans to engage in physical activity and exercise by becoming active for the first time, returning to exercise after a break in their routines, or building activity into daily routines. Go4Life offers exercises, motivational tips, and free resources to help participants get ready, start exercising, and keep going. The Go4Life campaign centers on an interactive Web site (www.nia.nih.gov/go4life), which features an evidence-based exercise guide in English and Spanish, exercise videos, and more. The initial partners include a diverse group of public and private Go4Life Team Members from major health and aging organizations and agencies, and the Institute intensified program activities in 2012.

Further, NIA produces informative, evidence-based educational materials for older adults, including "Age Pages" in English and Spanish on a wide variety of topics of interest, as well as more in-depth documents providing information and advice on an array of topics, including healthy nutrition, planning for retirement, and end-of-life care. Finally, NIA and the National Library of Medicine have created NIHSeniorHealth.gov, a health information Web site tailored to the specific cognitive and information needs of older Americans.

QUESTIONS SUBMITTED TO DR. HAROLD E. VARMUS

QUESTIONS SUBMITTED BY SENATOR JERRY MORAN

Question. Dr. Varmus, I have read several news articles about the impressive results being generated by the Cancer Genome Atlas project.

What is being done to ensure that the new information being discovered about cancer genomes will have direct benefits for patients?

Answer. The unprecedented wealth of data generated by the Cancer Genome Atlas (TCGA) is dramatically increasing our knowledge of the range and combination of abnormalities that may be found in cancer and refining our understanding of molecular pathways that control its malignant behavior. With the long-term goal of improving diagnostic precision and treatment outcomes for cancer patients, TCGA data are being applied to an array of projects and programs in the U.S. and abroad. For example, the National Cancer Institute (NCI) Cancer Target Discovery and Development (CTD2) Network, which is a consortium of investigators from many research institutions in the U.S., is elucidating new targets for therapeutic attack in cancer and developing means to inhibit these targets. TCGA data are also being used to explore the relationship between germline genetic variation and the molecular features of tumors that arise in various tissues.

TCGA data are widely available to qualified researchers through public databases designed to protect patient privacy, and we are continually striving to improve our management of these extremely large datasets through enhanced computational methods. The TCGA team provides extensive support to researchers who access TCGA data, including step-by-step protocols for how to locate and apply TCGA data, as well as preliminary data analysis to those who need assistance with manipulating the raw data, in an effort to maximize the efficient and effective use of the data. The large number of publications that use TCGA data (almost 400 since 2008) and the number of grant applications that include TCGA data (to date, more than 800) reflect the widespread availability and broad utilization of TCGA data by the cancer research community. In addition, the NCI is expanding its computational power in various ways to cope more effectively with the rapidly growing data sets from TCGA and other endeavors in cancer genomics.

Pursuing the genetic foundations of many cancers is a vital element of NCI's current research, comprising a substantial proportion of the institute's research portfolio. A principal task in the years ahead, for NCI and for the entire cancer research enterprise, will be to capitalize on the information developed through TCGA by supporting additional studies that validate and extend our understanding of—and ability to use to diagnostic, prognostic, and therapeutic advantage—the critical roles for specific genomic changes in tumors. Ultimately, these efforts can be expected to lead to more precise classification of cancers and more effective interventions that improve outcomes for patients.

Question. For example, are the data and the methods being incorporated into the design of NCI's clinical trials?

Answer. NCI has recently consolidated a number of its genomics initiatives—including TCGA and several pediatric cancer initiatives, most notably TARGET (Therapeutically Applicable Research to Generate Effective Treatments), as well as CTD2—into a single Center for Cancer Genomics. The new Center is working with other components of NCI and with other investigators in addition to those directly involved in TCGA to ensure that research findings are applied to developing new diagnostics and therapeutics that can be integrated into medical practice. For example, new therapeutic studies are now being designed by our clinical trials groups in conjunction with TCGA staff to match the genotypes of advancing cancers with targeted drugs and to seek genomic explanations for unexpectedly good responses to existing drugs or to not yet approved agents used in clinical trials; these studies will use methodology developed in conjunction with TCGA projects. In addition, several clinical trials have already been established based directly on TCGA data, and we expect additional trials to be initiated as TCGA continues to generate new information about potential targets for cancer treatment strategies.

We anticipate that our growing understanding of the molecular events that drive cancer development and distinguish one cancer type from another will have a marked effect on the way future clinical trials are designed. The new knowledge should enable the NCI cooperative groups that do most of our clinical trials to run smaller, more precise clinical trials with greater likelihood of therapeutic success. In addition, we can expect an increasing number of clinical trials that are somewhat tumor site-agnostic: directed at molecular vulnerabilities that are common to cancers that may arise in different tissues.

QUESTIONS SUBMITTED BY SENATOR RICHARD C. SHELBY

Question. Dr. Varmus, last year you expressed concerns about legislation that originally would have required the National Cancer Institute to spend $887.8 million of its budget on pancreatic cancer research. I share the concern about earmarking disease specific research. I believe science should dictate funding and a legislative mandate on disease specific research would lead to a slippery slope of Congress moving into the driver seat of determining how the National Institutes of Health (NIH) research funding is spent. That said, the current Administration has attempted to earmark NIH funding in the past for both cancer and Alzheimer's disease research.

How can it be wrong for Congress to direct funding, but not for the Administration to do so?

Answer. NIH is comprised of 27 institutes and centers (IC) mostly organized by specific diseases, organs, and stages of life. These entities come together to seek the fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

Historically, Congress has given NIH the flexibility to drive research and this flexibility has nurtured scientific advances and development of means to prevent and treat diseases more effectively. A baby born today can look forward to an average lifespan of nearly 79 years, nearly three decades longer than a baby born in 1900. For example, U.S. cancer death rates are falling more than 1 percent each year. and age-adjusted death rates from heart disease and stroke have fallen more than 60 percent in the last half-century. Thanks to anti-viral therapies developed by NIH funded researchers, HIV-infected people in their 20s can expect to live to age 70 and beyond.

NIH will continue invest research funds based on scientific opportunities and public health needs. As part of the Executive Branch, the NIH works closely with the Administration to plan future research efforts. The Administration's past interest in increased spending on cancer research and more recent interest in Alzheimer's disease (AD) research both came at a time of enhanced scientific opportunity and pub-

lic health need for progress against these devastating and common diseases. About half of men and a third of women in the U.S. will have a cancer diagnosis in their lifetimes, and cancer is the second most common cause of death. Moreover, research over the past three decades has transformed our conception of the disease, creating opportunities for rapid advances Thus we have learned that cancer is a disease of the genome, that it's not just one but many diseases, and that investments to use the new tools of genomics are likely to lead to rapid progress in the diagnosis and treatment of those several diseases. For example, as drugs are developed that target certain mutations, doctors will be able to use information about the molecular profile of a patient's tumor to assess whether a given drug is likely to be effective. Genomic knowledge can also be used to decide against a particular treatment, if the appropriate target mutations are not in play, thus sparing a patient the costs, waste of time, and side effects of a drug that is not likely to help them.

The number of individuals with AD is expected to increase dramatically as the population ages. The U.S. Census Bureau estimates that the people 65 years and older will double to about 72 million during the next 20 years. As the population ages, the medical and treatment expenses associated with AD will continue to increase and impose a significant economic burden to society and the government. At the time the Administration announced the additional funding for AD, NIH seized the opportunities to expand on several AD advances. NIH supported researchers discovered that higher amounts of the brain amyloid deposits in dementia-free individuals were associated with an increased risk of developing dementia over time, making it a possible preclinical sign of disease even among individuals who appear mentally normal. In addition, NIH supported researchers developed a method of testing for the known biomarkers for AD in the cerebrospinal fluid. With these discoveries, NIH hopes to help diagnosis individuals with AD in order to initiate treatment efforts early and delay the progression of AD.

Question. It is my understanding that you had numerous concerns about authorizing legislation proposed last year that would have specified an amount of funding for pancreatic cancer. Can you discuss some of those concerns?

Answer. The National Cancer Institute (NCI) raised serious objections last year to a legislative proposal (a version of H.R. 733, filed originally on February 16, 2011, "to provide for a Pancreatic Cancer Initiative"). However, our objections were directed largely against a new methodology that would have altered how NCI funds grant applications.

In this instance, the legislation would have required that the Secretary of Health and Human Services convene a group, composed almost entirely of pancreatic cancer researchers, to recommend which grant applications should be funded. This would have created an unfortunate precedent for many groups to ask for similar privileges, a situation that would have been unworkable and damaging. Fortunately, this and several other objectionable elements were removed from H.R. 733 before its eventual approval as the Recalcitrant Cancers Act.

Although we objected to the bill in question largely on other grounds, the NCI generally disapproves of mandates to spend specific amounts of money on individual cancers. This is so for several reasons. First, it is difficult to determine an exact number for disease-specific spending: some studies address multiple cancers; many are aimed at fundamental cell processes that are relevant to most or all cancers; and some grants support training, technology development, and other infrastructural issues that cannot be classified. More importantly, history has supported the argument for supporting the best science, rather than meeting a fiscal quota for each disease type. It is common for studies of one type of cancer to provide unanticipated insights into another type or for studies of the basic features of cancer to illuminate our understanding of a variety of cancers. For example, investment in a rare disease, retinoblastoma, was critical for the discovery of tumor suppressor genes, a class of genes that is affected in essentially every cancer type. 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. What has worked best is the support of experiments that pursue the most inviting scientific opportunities. Of course, the NCI is attentive to its patterns of spending on many types of cancer, especially with regard to clinical research; but rigid prescriptions for funding levels limit the Institute's capacity to support the most productive work and respond quickly to new developments in cancer science.

SUBCOMMITTEE RECESS

Senator HARKIN. The hearing of the Labor, Health and Human Services Subcommittee is adjourned. Thank you again all very much.

[Whereupon, at 4:20 p.m., Wednesday, May 15, the subcommittee was recessed, to reconvene subject to the call of the Chair.]