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UNLOCKING THE CURES FOR AMERICA'S MOST DEADLY DISEASES

HEARING

BEFORE THE

SUBCOMMITTEE ON SPACE, SCIENCE, AND COMPETITIVENESS

OF THE

COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION
UNITED STATES SENATE

ONE HUNDRED FOURTEENTH CONGRESS

FIRST SESSION

JULY 14, 2015

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SENATE COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION

ONE HUNDRED FOURTEENTH CONGRESS

FIRST SESSION

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UNLOCKING THE CURES FOR AMERICA'S MOST DEADLY DISEASES

TUESDAY, JULY 14, 2015

U.S. SENATE,
SUBCOMMITTEE ON SPACE, SCIENCE, AND COMPETITIVENESS,
COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION,
Washington, DC.

The Subcommittee met, pursuant to notice, at 10:07 a.m. in room SR–253, Russell Senate Office Building, Hon. Ted Cruz, Chairman of the Subcommittee, presiding.

Present: Senators Cruz [presiding], Wicker, Fischer, Johnson, Peters, and Udall.

OPENING STATEMENT OF HON. TED CRUZ, U.S. SENATOR FROM TEXAS

Senator CRUZ. Good morning. This hearing will come to order. We are here today to discuss an issue that is important to every one of us. We are here today to discuss cures—cures to life threatening diseases, cures to diseases that devastate the lives of millions.

We are here today to discuss what we are doing well and what we could be doing better to open new frontiers.

The United States has led the world in path-breaking medical research and yet there is far more we could be doing.

In the year 2015, it is estimated almost 600,000 Americans face cancer. Another 700,000 with Alzheimer's Disease are expected to die this year. Nearly 500,000 people in the United States suffer from the effects of Parkinson's Disease. 795,000 suffer strokes each year. 25.8 million people are afflicted with diabetes, and 95 percent of other rare diseases currently have no recognized treatments or cures, leaving most of the 30 million patients afflicted by them with few or no options.

The path to achieving medical breakthroughs in cures is long and capital intensive. Often it seems when it comes to medical research we are pennywise and pound foolish, that we pay billions or trillions on the back end, dealing with the consequences of horrific diseases, rather than investing and creating the incentives on the front end to cure these diseases once and for all.

The average cost to get a single drug approved by the FDA is between $1 billion and $2 billion. In addition, the regulatory burdens and bureaucratic unpredictability slow the ability of innovators to create new cures. Regulatory burdens and uncertainty are also having an effect on private investment.

In 2011, the National Venture Capital Association issued a report confirming that U.S. venture capitalists are reducing their investments in biotechnology and medical device companies, and are shifting their focus overseas to Europe and Asia, primarily due to the persistent regulatory obstacles of the FDA.

Despite these daunting and persistent challenges, I continue to believe that incredible American ingenuity still has the power to fuel a revolution and open medical breakthroughs.

As former FDA Commissioner Andrew von Eschenbach has stated, "We stand on the cusp of a revolution in health care. Advances in molecular medicine will allow us to develop powerful new treatments that can cure or even prevent diseases like Alzheimer's and cancer."

As we begin a discussion this morning on how we can unlock cures for America's most deadly diseases, we will take a global look at examining how the American regulatory system compares with the rest of the world, and how incentives can change so that in the coming years we have more and more breakthroughs rather than less and less bureaucratic inertia.

Whether it is increased Federal funding through direct medical research, whether it is using tools such as prize competitions, whether it is intellectual property reform or easing the burdens for approving new drugs and medical devices, all of those are steps that are going to need to be examined closely if we are going to take major steps toward new cures.

American poet Robert Frost once stated "Freedom lies in being bold." That is the approach all of us hope we take, that it is in that spirit that I welcome our panel of distinguished experts and friends to engage in a discussion of creating bold solutions that will enable medical discoveries to cure and to prevent deadly diseases.

Senator Peters?

STATEMENT OF HON. GARY PETERS,
U.S. SENATOR FROM MICHIGAN

Senator PETERS. Thank you, Mr. Chairman. Thank you for convening this hearing, and thank you to a very distinguished panel to talk about a very important issue for me and I think for the whole country.

Without question, scientific discovery and technological breakthroughs drive our understanding of the world, from the airplane to the MRI to the Internet, innovations in science and technology have transformed the United States from a rugged frontier nation to a global economic super power.

Even today, U.S. researchers continue to search for the next big thing, that game changing innovation that will spark new industries, create jobs, build the economy, and further the United States' technological leadership.

The Federal Government is helping lead the way. Investments from the National Science Foundation, the National Institute of Standards and Technology, the National Institutes of Health, NASA, and other Federal agencies work across a broad range of science and engineering topics to help educate a world class science and technology workforce and bring us continuously closer to breakthrough innovations.

A few weeks ago, I had the privilege of joining some of our nation's brightest minds at a panel discussion by the Science Coalition. We looked ahead to the year 2034 and imagined some of the exciting discoveries that could be possible based on Federal investment into basic research.

One panelist was working to develop a new class of regenerative drugs that would provide effect treatment for diseases like Parkinson's and Alzheimer's. Her work was supported by the NIH. Another was working to develop safer and quicker produced vaccines in pill form, enabling us to keep pace with multiplying infectious disease threats. Her work has been supported by both NASA and the NSF.

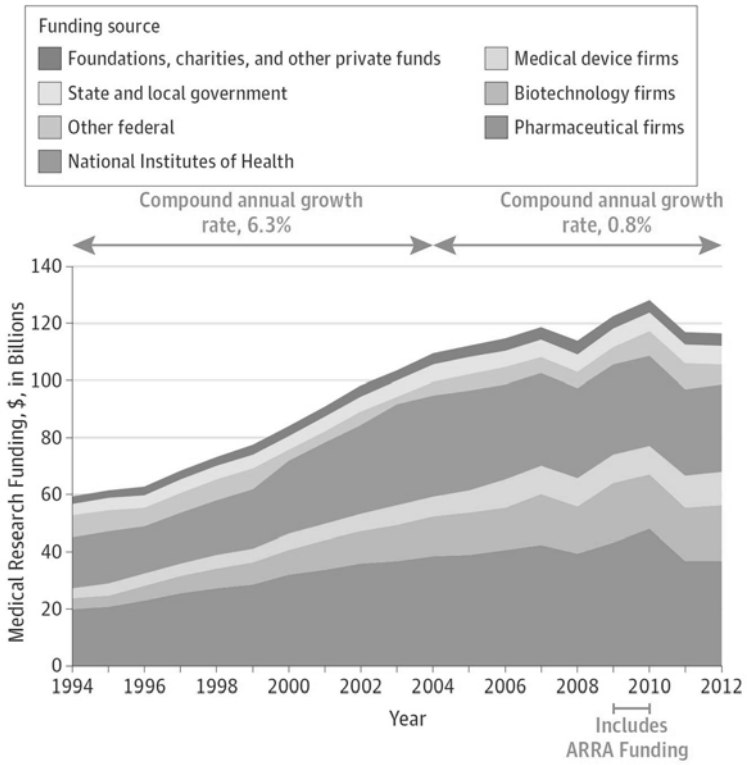
These examples are just a small part of a long history of critical Federal Government support for research and development.

Tragically, however, overall Federal R&D spending has fallen to below 1 percent of GDP. This is unacceptable. When we examine global funding trends in biomedical research, we see that private investment in the U.S. has begun to fall off as well. In fact, Mr. Chairman, I have a chart that highlights that that I would like to enter into the record with unanimous consent.

Senator CRUZ. Without objection.

[The chart referred to follows:]

U.S. Funding for Medical Research By Source, 1994–2012



Source: Hamilton Moses III, MD, *et al., The Anatomy of Medical Research: U.S. and International Comparisons,* Journal of the American Medical Association, 2015.

Senator PETERS. Studies point to a number of contributing factors to this fall off. For one, some private companies are shifting their research overseas due to the availability of foreign government incentives and access to well educated and relatively inexpensive science and technology work forces.

If we look more closely at these global funding trends, particularly for the past 20 years, one conclusion is abundantly clear, private investment in the U.S. correlates very closely with government investment. When government investment in R&D shrinks or stagnates, the private sector pulls back as well. When the government grows its investment, the private sector follows suit.

The trends are clear and so are the actions that we must take. First, we must develop our science and technology workforce through education, inspiration, and opportunities. Companies looking to perform innovative breakthrough research will go where the talent is. We need to make sure that our science and technology workforce is second to none.

Second, Federal investment in science and technology must at least keep pace with the growth of our economy. If the stagnant trend we have seen in the last few years is allowed to continue, the buying power of our Federal research budget will slowly erode with inflation and private investment will shift overseas in search of greener pastures.

Third, we need to keep our Federal research portfolio balanced. The challenges of our age are increasingly interdisciplinary in nature from biomedical science to behavior research to space exploration. Only a broad and balanced science and technology investment portfolio will preserve America's place at the forefront of innovation for generations to come.

Finally, we need to find creative policy avenues to incentivize breakthroughs and reduce barriers to innovation.

The University of Michigan's fast forward medical innovation program is an example of the right step to take. Funded by NIH, this program is nurturing commercialization in entrepreneurship with the ultimate goal of getting more medical devices, diagnostics, therapeutics, and health information technologies to the market sector.

We cannot forget that we are in constant competition with other nations that have learned from our example and are rapidly growing their commitments to scientific research.

Now is not the time to slow down. We have to step up in Congress on both sides of the Capitol and on both sides of the aisle to strengthen our commitment to basic research, to education, and to translating new knowledge into the next big thing.

Thank you, Chairman Cruz, for holding this hearing today, and I would like to thank all of our panelists once again for appearing before us. I certainly look forward to both your testimony and the discussion to follow. Thank you.

Senator CRUZ. Thank you, Senator Peters. I would now like to welcome each of our distinguished panelists. We begin with Dr. Tom Coburn, who is a friend to each of us here. It is good to see you, Tom. Welcome back, you are looking good.

Dr. Coburn has had an extraordinary career. He began his career as Manufacturing Manager at the Ophthalmic Division of Coburn

Optical, which under his leadership grew from 13 employees to more than 350. He captured 35 percent of the U.S. market.

He then became a medical doctor and has personally delivered more than 4,000 babies. He was elected to the U.S. Congress and served from 1995 to 2001, and he served as a colleague of ours in the U.S. Senate from 2005 to 2014. He was an extraordinary leader in this body and is a good friend.

Our next witness is Christopher Frangione, who is the Vice President of Prize Development at XPRIZE. He brings more than 15 years of experience in the strategy and operations fields with energy companies and as a management consultant.

He received a Bachelor of Arts from Colby College and a Master in Business Administration and Master of Environmental Management from Duke University.

Our next witness is Mr. Peter Huber, Senior Fellow at the Manhattan Institute. Mr. Huber is an author of numerous books including "The Cure in the Code, How 20th Century Law is Undermining 21st Century Medicine," and "Orwell's Revenge, The 1984 Palimpsest," and I am not sure what that book is about, but it is apparently on Facebook CEO Mark Zuckerberg's 2015 reading list.

Mr. Huber has had a remarkable career as well serving as Associate Professor at MIT, clerking for both Ruth Bader Ginsburg when she was a judge on the D.C. Circuit and then Sandra Day O'Connor in the U.S. Supreme Court, and he is a partner at the Washington, D.C. law firm of Kellogg, Huber, Hansen and Todd.

Finally, Dr. Keith Yamamoto, Vice Chancellor for Research, University of California, San Francisco. Dr. Yamamoto received his Ph.D. from Princeton University, my alma mater. He is also a Professor of Cellular and Molecular Pharmacology at the University of California, San Francisco.

Throughout his career, Dr. Yamamoto's research has focused on signaling and transcriptional regulation by nuclear receptors. He uses structural, mechanistic, and systems approaches to pursue these problems in molecule cells and whole organisms.

Dr. Yamamoto also chairs the Coalition for the Life Sciences, and he serves on the Advisory Committee for the Division of Earth and Life Studies for the National Academy of the Sciences.

The Committee is honored to have such distinguished experts with us, and we welcome you, and we will begin, Dr. Coburn, with you.

STATEMENT OF TOM COBURN,
FORMER U.S. SENATOR FROM OKLAHOMA

Dr. COBURN. Thank you, Mr. Chairman and Senator Peters for inviting me. I just want to give a little background. I am probably the only person in the room that has been subjected to FDA controls as a manufacturer. I remember when Gerald Ford signed the Medical Device Act. Two, has had manufactured products under FDA's guidance, and used their products as a physician after approval and saw the high cost and delayed onset of many products not just medical devices.

Three, have been a patient, and very interested in what is happening in terms of modern medicine, especially in terms of breakthrough technologies because it becomes very personal when you

have advanced cancer, that new breakthroughs and new methods of approving new drugs are very important.

Finally, as a practicing physician, seeing the interaction between family and patients with Alzheimer's, and knowing that if we had breakthroughs in those areas, the tremendous difference not just in family interaction and family costs and family effort, but also in terms of economic costs and economic effort to our country.

I just want to put in perspective, I have kind of been all around the FDA, and as a legislator, and I would point you to a couple of things. Number one, the last piece of major legislation was FDASIA, and I would ask you to go look at what FDA has done, what Congress has mandated and signed by the President three years ago, and what you will see is not much, even though you mandated that things be done.

Whatever we do, the 21st Century Cures Act is a good start that came from the House. It needs to be refined and perfected. It is a bipartisan bill. That is what ought to come out of the Senate, a real look at what we can do and cover all the bases.

I want to make four main points with you today and I will finish, my testimony has obviously been available to you.

The first point I would make is technology is moving power back to patients and physicians, not to the FDA. No matter what you do, more and more decisions are going to be made outside of government regulation, because that is where the science and technology has taken us.

We need to incentivize breakthrough innovations, not just incremental advances against major diseases like Alzheimer's. They need to be incentivized.

I will give you a great example, and I was involved in this. In the AIDS epidemic, what happened at FDA? A large group of people who were extremely interested in seeing the process speed up and cures come to fruition demanded the FDA, not Congress, but activists demanded that the FDA respond. Guess what they did? Today, we have a chronic disease instead of a life killing disease. That did not come through Congress. That came through activists being persistent in pushing a regulatory agency.

The barriers that Congress faces in addressing FDA reform are often self created, you create them. Let me give you a great example. The FDA did a wonderful job on the approval process of the drug, Vioxx. They did not make one mistake, according to their approvals. There is no way you can be perfect 100 percent of the time in what we have set up for a regulatory regime for new drug approvals, but what came out of Congress on Vioxx? Tremendous beating up of the FDA.

If any of us had been running the FDA, running it per protocol as it should have been, we would have done exactly the same thing, except Congress beats them up.

The other thing with Vioxx is nobody ever thought about the millions of people who were back at work because they did not have chronic pain anymore because of Vioxx. Everything is a balance.

We have lost a great drug that had a rare side effect and the trial bar got a hold of, but you have millions of people now who do not have available a drug that allows them to go to work every day that is not a narcotic.

We sometimes as Members of Congress are our own worse enemy in terms of beating up the FDA. What happens when the FDA hears that, it makes them less likely to take a chance on something that could be very, very beneficial to the country because if there is a consequence of something going wrong, then they want to protect the agency, and they do not want to hear the screams that come from Congress.

The third point I would make is reimbursement and intellectual property reforms that reward breakthrough medicines that are curative and offset other types of health care spending are just as critical as FDA reform.

Payment reforms and intellectual property reforms, you can change the FDA, but if you do not change the payment reforms, and if you do not change the intellectual property reforms, one of the reasons drugs are failing in this country today is people do not know that if they invest capital that they will still have any capital left to take advantage of intellectual property when they get through the process, because the process takes so long.

That needs to be a thought if we really want to get new advances, and we really want to hurry up to cures, not just improvements but cures, then what we have to do is change intellectual property and we have to change the way we pay for it.

For example, 12 years of data exclusivity, not talking about patents, talking about bringing exclusive data to the FDA, say we have a new breakthrough on a biological marker, here is the way this works, we have the data, protect it.

Then what you have is capital invested. We are losing capital investment in this country because of the questionable nature of whether or not you will be able to take advantage of that capital investment, because the intellectual property will not be covered.

Finally, transparency and peer engagement is one of the most effective tools we have for rapidly advancing science and reducing FDA's risk aversion.

I do not blame the FDA for being risk adverse, the way Congress treats them. I do not blame them. It would be really courageous to ignore what Congress has to say to them since you control totally their budget outside of some of the small advancements.

In the field of biomarkers, if we force the FDA to become collaborative and cooperative and transparent, you are going to see things move at a very rapid pace in this country. If you allow the FDA to continue to not be cooperative, continue to not be transparent, and continue to not be collaborative when it comes to biomarkers, you are going to see all this industry and all this intellectual property go outside of this country.

The 21st Century Cures legislation is a great move towards that, but it has to be better. It has to have some teeth in it to force the FDA to become transparent, to be collaborative, because they have not been. If we do that, what you will see is a marked move forward in terms of advances in cures for new diseases, not just treatments but cures, and the identification of new pathways, and it will build on itself.

It is happening now, and it is going to continue to happen because private capital, massive computing, and great medical record searching right now is causing us to find new treatments all the

time with existing drugs, repurposing drugs, and we are going to see more of it. If the FDA becomes a block to that, then we are in trouble.

Finally, the concern of regulators and even policy makers is too often about what might happen if something goes wrong. Something is already deeply wrong in our country. Millions of Americans are suffering and dying from untreatable diseases or the lack of better treatment options, not because it has to be that way but because we have a regulatory scheme that makes it that way.

Too many medicines or medical devices are never developed because it takes too long and costs too much to bring them to patients.

We need a drug development system that encourages innovators to pursue breakthrough cures and allows patients and physicians fighting serious illnesses to take informed risks when we have good information about the mechanistic effects of drugs and the relationship to known causal pathways, and allows everyone to learn from the real world evidence about drug safety and efficacy.

That is not the system we have today but it is the one we need to face the health and fiscal challenges for our future.

The double blind placebo controlled study in the future will have very limited value to us if we want to propel our country ahead in terms of leading on new innovation and new cures.

Thank you. I would be happy to take your questions.

[The prepared statement of Dr. Coburn follows:]

PREPARED STATEMENT OF TOM COBURN, FORMER U.S. SENATOR FROM OKLAHOMA

First, I'd like to thank Chairman Cruz, Ranking Member Peters, and the other members of the Committee for inviting me to speak today about an important subject that is near and dear to my heart: advancing cures for the tens of millions of American patients and their families battling life threatening or disabling disorders.

The battle is personal for me in many ways. As a physician, I see elderly patients suffering from symptoms of early dementia, and eventually Alzheimer's, without a real treatment in sight. The burden of the disease falls not only on patients, but on their families and caregivers. Their plight is agonizing. And I can't offer them any effective treatments.

As a three-time cancer survivor, I'm excited by the progress we've made against this deadly disease, but also mindful of how much further we have to go to conquer it. Cancer remains the second leading cause of death in the U.S.; for patients diagnosed with metastatic solid tumors—of the lung, colon, pancreas, or ovaries—far better diagnostic and treatment options are desperately needed. Diagnosing these diseases late—as we do all too often today—means that we can only delay the inevitable, at great human and financial cost.

But I'm also deeply optimistic, because I've seen firsthand the inventiveness, dedication, and entrepreneurship of America's leading researchers and companies. I'm watching a flood of new information emerge that is helping researchers map out cancer's vulnerabilities at the genomic level and develop personalized treatment programs for patients tailored to their unique tumor profile. These approaches are being made possible by advanced computing platforms for rapidly sorting through this torrent of information, guiding doctors and patients to the best treatments. For instance, IBM's Watson is analyzing millions of journal articles, patient records, and data on approved and experimental drugs to help developed personalized cancer-care regimens faster than any single physician alone could ever do. Watson and other "big data" and machine-learning approaches are literally getting smarter every day—and will, one day, expand state of the art oncology services to every cancer patient in America in their own communities, not just patients with access to leading cancer centers.

The advent of systems biology and, more recently, quantitative systems pharmacology are helping us unravel the molecular networks of complex diseases at an unprecedented pace; simulate the effects of candidate compounds in computer models;

weed out drugs likely to fail; and identify those most likely to succeed, all before a single human patient is dosed. Companies are also perfecting the art of developing targeted medicines, including genetically modified T-cells, monoclonal antibodies, and new gene-editing technologies. This approach heralds a day when researchers will use molecular scalpels to target disease-causing cells and genes—and kill or replace them with healthy versions.

Is this the Golden Age of Medicine? Not yet. How long it takes us to get there rests with you. It depends on the 21st Century Cures legislation just passed by the House, on steps that you can take to improve it even further, and on decisions that Congress will make over the next few years to enhance the climate for breakthrough innovation in the United States.

The way we approve new medicines and diagnostics must change. It's got to be completely transformed. I know that word is overused and we've been talking about transformation for a long time. We don't need another committee to study it, or hold another conference about it. We need to do it.

I'm honored today to be testifying beside Keith Yamamoto, vice chancellor for research at UCSF, one of America's leading medical-research universities. He is one of the visionary leaders of the precision-medicine movement, and one of the architects of the pivotal National Academy of Sciences committee report *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease.* That report talked about the need to develop a true molecular taxonomy of disease through a knowledge network that patients and physicians could consult and upload information to in real time—moving us away from an outdated classification of disease based on clinical symptoms and toward one based on molecular pathways.

We've made and continue to make rapid progress toward precision medicine. But the way the FDA approves new medicines is still mostly rooted in those clinical signs and symptoms. It is based on cutting edge science—cutting edge in 1962, when we couldn't identify the molecular mechanisms of disease, let alone design drugs to target them. It's how we got the double-blind, placebo-controlled trial (preferably two of them) as the "gold standard" for approving new drugs. That gold standard is increasingly out of date, as we gain confidence that we actually are targeting the pathways causing the disease or disorder in question. And we can also design trials that, as they proceed, help unravel those pathways in a learn-as-we go strategy using targeted medicines. We can't continue to ask one narrow question at a time, in one trial at a time. The current drug development and approval system is too expensive, too time consuming—and, frankly, likely unethical when there are better approaches available.

What we should be doing instead is ensuring that all trials that we run attempt to match new medicines to the biology of the patients taking the medicine: we know that different patients with the same clinical symptoms can respond differently because of a variety of genetic factors that affect drug metabolism (or indicate that one patient actually has a totally different disease that needs a different treatment).

We're moving in this direction—rapidly in cancer and much more slowly for other indications. Far too many drugs are still tested and developed based on 1962-era science. It's a one-size-fits-all approach to innovation that causes too many drugs to fail that could succeed if they were tested in the correct order, in the correct groups of patients.

While the FDA remains concerned about approving ineffective or dangerous drugs, alternative approval pathways—based on molecular signatures called biomarkers, followed over time in patient registries via electronic medical records—could bring potential treatments to desperate patients much sooner, with appropriate requirements for post-market trials verifying long-term safety and efficacy. That approach is the exception today but should be the rule. Despite its best intentions, and despite repeated pronouncements since 2004, it's clear that the FDA isn't embracing clinical-trial transformation to the degree that it could. The rapidly falling cost of genetic testing, the ability to share tens of thousands or hundreds of thousands of detailed patient medical records and the rise of analytic infrastructure, "bioinformatics," that can rapidly comb through massive, complex datasets all make it increasingly possible for individual physicians to develop personalized treatment profiles that leap ahead of the FDA's approved drug labels—which might be years or decades out of date.

In 2013, researchers at Stanford University screened FDA-approved drugs with known molecular targets, with the molecular expression profiles of known tumor types. They found a match between a 50-year old class of anti-depressants and small cell lung cancer. They then tested the drug in cancer cell lines and animal ok models, and found that the match predicted by their software killed tumor cells.

It turned out that the anti-depressants caused certain cancer cells, called neuroendocrine tumors, to self-destruct, through a process called apoptosis.

Neuroendocrine tumors are found in subsets of other types of cancer, including pancreatic cancer, so the drugs may be effective there as well. The drug quickly went into mid-stage efficacy testing in small cell lung cancer, potentially shaving years off development timelines. Atul Butte, now a colleague of Dr. Yamamoto's at UCSF and one of the developers of this drug repurposing strategy, observed:

> "We are cutting down the decade or more and the $1 billion it can typically take to translate a laboratory finding into a successful drug treatment to about one to two years and spending about $100,000."

That's tremendously exciting; but imagine if we could do this at scale. By scanning millions of real-world patient profiles, researchers might discover that some patients, "exceptional responders," are already being cured with off-label drugs, or rehabilitate medicines that the FDA considers "failures" in broader populations. Researchers could also discover evidence that patients who take certain types of commonly prescribed drugs (statins, newer classes of anti-depressants, etc.) have lower rates of some types of cancer or Alzheimer's, making them powerful off-the-shelf options for preventing or treating chronic illnesses. With enough data, the right analytics, and the correct strategy for adaptive clinical-trial designs, researchers can unravel the right time and sequence for using existing or experimental treatments to produce better outcomes and even cures.

In short, we can harness the many petabytes of data we're already collecting to discover, test, and validate new treatment approaches without waiting for the FDA's overly cautious bureaucracy to catch up. Properly harnessed, data can deliver new treatments and cures at a fraction of the time and cost required by the FDA's 50-year-old paradigm for testing new drug candidates.

To revolutionize outcomes for patients, Congress must require the FDA to collaborate with the broader scientific community to establish clear guidelines for unleashing the full potential of digital medicine to transform drug development and enable precision medicine prescribing by physicians. Congress must set overarching goals for all Federal agencies that touch digital medicine, especially the NIH and HHS: streamline bureaucracy, reduce waste, and coordinate research efforts, and hold agencies accountable for doing so through annual or biannual performance reports.

We need reimbursement reforms that reward breakthrough innovations. Many curative technologies will be very expensive at first, but will save the health care system vast amounts of money in the long run by reducing hospitalizations, use of nursing homes, and the need for repeat physician visits and tests. A one-shot cure for leukemia or sickle-cell anemia may be extremely expensive by historical standards, but may still be extraordinarily cost effective for public and private payers in the long run. New approaches to funding and paying for those breakthrough treatments will be needed if we are to address our massive entitlement spending challenges for Medicare and Medicaid. A cures strategy is a strategy that fiscal conservatives should embrace, as long as we are truly paying for outcomes.

Don't mistake my optimism for naiveté. There are real challenges we have to overcome to embrace a cures strategy for American health care. Existing electronic medical records, for instance, don't capture much of the data we need to support rapid development of personalized medicine protocols. Many physicians still are not well-equipped to interpret results from genetic testing. While Medicare has required EMRs for reimbursement purposes, they haven't helped streamline the physician's workload or enhance patient care. If anything, they've detracted from it.

But these challenges are largely engineering problems—problems amenable to technical solutions. The basic tools enabling precision medicine are available and are widely used across the Internet, as well as in numerous industries, from retail to the Department of Defense. (The Defense Advanced Research Agency is building a machine-learning engine to identify and predict all of the genes and signaling networks driving all cancers.) Several large hospital systems, such as Intermountain Healthcare, are developing sophisticated electronic-records systems and diagnostics platforms that can serve as proving grounds for rapidly scaling up new digital medicine strategies, as well as for sharing such data.

What will it take to enable a cures strategy for America? There are many good ideas in the 21st Century Cures legislation; but the biggest one is yet to be embraced. The FDA will have to pivot from being a gatekeeper to a collaborator, one that works with many stakeholders to develop evidentiary standards for enabling digital, precision medicine on a national scale. Power will have to shift from centralized bureaucrats to empowered patients and physicians. But I have no doubt that the country that brought us Google, Intel, Amazon, and Salesforce can tackle the

challenge of disrupting the FDA's nearly 50 year-old framework for advancing innovation.

Regulators will resist—just as they resisted the demands of AIDS activists in the late 1980s. Yet now, as before, when successes accumulate, regulators will take credit for embracing reform.

By sending the 21st Century Cures legislation to the Senate, Congress has taken one powerful stride to advance precision medicine. Your responsibility is to put your own stamp on the legislation, to ensure that the transformational potential of digital and precision medicine is realized for patients as swiftly as possible.

Senator CRUZ. Thank you, Dr. Coburn. Mr. Frangione?

STATEMENT OF CHRISTOPHER FRANGIONE, VICE PRESIDENT, PRIZE DEVELOPMENT, XPRIZE

Mr. FRANGIONE. Thank you for having me today. I would like to thank the Committee, Chairman Cruz and Ranking Member Peters, for the opportunity to testify today.

We welcome the Committee's attention to solving cures, and more importantly we welcome your attention to learning about how and when prizes could be one of those tools in helping find cures.

I am the Vice President of Prize Development at XPRIZE Foundation, which means my team designs the prizes and brings them to launch, and then we hand them off to the operations team.

We are the global leader in the creation of incentivized prize competitions. We are a 501(c) non-profit organization. Our mission is to bring about radical breakthroughs for the benefit of humanity, and we do this by shining a global spotlight on the problem, and incentivizing people from around the world, and that is important, from around the world to solve that problem by offering a multi-million dollar purse. We do not care where you live, where you went to school, or what you have done before.

Some of our cures can be figured out by somebody that has none of the experience that anybody in this room has, and we believe in that. To date, we have awarded five prizes ranging from highly fuel efficient vehicles to oil spill clean-up and health, worth over $27 million, and we have five active prizes right now worth over $64 million, including our recently launched Barbara Bush Foundation Adult Literacy XPRIZE focused on developing mobile applications for U.S. adult learners that are illiterate.

We also have a health prize in our Life Sciences Group, and that is our $10 million Qualcomm Tricoder XPRIZE. This is to create a device that can diagnose your health without a panel of doctors any time, anywhere.

We are actually in our testing stages of that right now, seven teams delivered 30 prototypes that were actually tested on consumers. The idea is that the winning team that most accurately diagnoses a set of disease states without a health professional, really allowing you to take care of your health, and know when it is important to go see a doctor or when you can just stay home.

One of those top seven—they are from four countries—is a team of undergraduates from Johns Hopkins University. Some of them are industry players and some are from outside the industry.

We are seeing a lot of successes in prizes in the health space but there are only a few places where prizes really work in health and there are places where prizes do not work in health. I will quickly highlight those.

Where they do work is where new forms across disciplinary collaboration is needed, by bringing people together that would not otherwise speak to each other or work together, bringing the FDA and the innovators together, or where research is under funded or there is a small patient pool driving inefficient market activity, or where an engineering type solution can come to bear.

I will give you an example. We are working with the American Society of Nephrology on a kidney disease prize. It is a technology prize to give better patient experience to folks and help solve the problem. That is an engineering type prize. You can imagine wastewater engineers or people from completely outside the industry coming together to solve that problem.

Where we do not think prizes work, it is where early stage research and discovery is needed, that basic research that Ranking Member Peters was talking about. It is too hard because the teams are looking for that end market and they are going to spend too much money and too much time getting there, or where these large longitudinal studies are needed. If there is a way to bypass those, a prize would be able to work better.

Even where we believe prizes work well, they can always complement traditional forms of funding and should never replace them.

We are also currently exploring a prize in Alzheimer's. We are working with 10 individual donors, and Senator Wicker has a keen interest in this, and we thank you for that. We have been working with his staff on how do we partner on that.

Prizes are powerful for many reasons. You can leverage your investment. If you go and put out a $5 million grant, you are going to get $5 million worth of work. If you put out a $5 million prize, you can expect to get $20 million to $50 million worth of work because the teams are spending their own money. You are democratizing innovation. You are bringing in those outside innovators I talked about, people you would never give a grant or contract to because you wouldn't think they were going to be successful.

We find that we do not care if you have 20 years of experience or 20 days of experience, as long as you solve the problem, you win.

Prizes allow you to reduce your burden of risk. You are putting a lot of risk on the teams. The teams are spending their own way and you are only paying for success. In order for prizes to work, you have to design them well, and this is where we want to help the government do better.

The teams are not competing for the prize purse. They know that only one, two, or three teams are going to get the prize purse. They are competing for that end market. What can you do to help them get to the end market in terms of education, business plans, road shows, in terms of testing, what can NIH do for them that would cost them lots of money or somebody else, or in terms of access to funders or whomever?

We believe that prizes work really, really well when you have great partners. I will highlight one that we actually have with the FDA. We have a partnership with the FDA on our Qualcomm Tricoder XPRIZE where the FDA has volunteers that will actually answer the phone when our teams call to help them understand what they should expect. It is all off the record, but it gets the

teams from outside the industry some understanding of what would happen next in the regulatory process.

For prizes to work, you really need to offer these additional incentives.

In summary, we believe that the public and private sectors must work together to utilize every tool available, and prizes are one of those tools. It is not the only tool, but it is a really, really powerful tool you can use.

Thank you.

[The prepared statement of Mr. Frangione follows:]

PREPARED STATEMENT OF CHRISTOPHER FRANGIONE, VICE PRESIDENT, PRIZE DEVELOPMENT, XPRIZE

Introduction

On behalf of XPRIZE, I'd like to thank the Committee, Chairman Cruz and Ranking Member Peters for the opportunity to testify today. XPRIZE welcomes the Committee's attention to incentivizing cure development for the world's deadliest diseases. XPRIZE welcomes the conversation regarding how and when prizes can be an appropriate and effective mechanism for the Federal Government to incent innovation, economic growth and solutions to some of the biggest problems facing our Nation today. I'm Chris Frangione, Vice President of Prize Development. I am responsible for overseeing the design of XPRIZEs from conception to launch.

Background

XPRIZE is the global leader in the creation of incentivized prize competitions. As a 501c(3) not-for-profit organization, our mission is to bring about radical breakthroughs for the benefit of humanity, thereby inspiring the formation of new industries and the revitalization of markets. XPRIZE works to accelerate the pace of innovation across sectors through the implementation of prizes that are audacious, yet achievable. XPRIZE looks to find "white spaces" where breakthroughs can bring about exponential shifts.

Founded in 1995, we are the recognized world leader for creating and managing large-scale, global, incentive prize competitions that stimulate investment in research and development worth far more than the prize itself. To date, XPRIZE has successfully awarded five prizes with combined purses of over $27 million. These prizes spanned multiple sectors, including Progressive Insurance Automotive XPRIZE for highly fuel-efficient vehicles, the Wendy Schmidt Oil Cleanup XCHALLENGE for better surface oil cleanup technologies, the Northrop Grumman Lunar Lander XCHALLENGE, the Nokia Sensing XCHALLENGE, and of course the Ansari XPRIZE for commercial space flight. In most of these competitions, we collaborated with the U.S. government, the private sector, and the research community.

We also have five active prizes with combined purses of $64 million. These include the $30 million Google Lunar XPRIZE that challenges teams from around the world to land a rover on the Moon and send back live video; the $2 million Wendy Schmidt Ocean Health Prize—a competition to create breakthrough pH sensors that can help us begin the process of healing our oceans; the $15 million Global Learning XPRIZE that challenges teams to develop new learning solutions to empower children and communities around the world; and the $7 million Barbara Bush Foundation Adult Literacy XPRIZE, which challenges teams to develop mobile applications for adult learners that radically improve their literacy skills in just twelve months.

Life Sciences

Specific to today's discussion, XPRIZE has a Life Sciences Prize Group aimed at stimulating innovative breakthroughs in molecular biology, stem cell research, bionics, organogenesis, synthetic biology, and artificial intelligence in order to improve health care and extend healthy living. XPRIZE seeks to accelerate the real-world impact of science, technology, and information related to the worldwide optimization of health and the elimination of illness and disease.

We recently awarded $2.25 million to competition teams for the Nokia Sensing Challenge, a medical sensor challenge aimed at accelerating the availability of hardware sensors and software sensing technology that individuals use to access, understand, and improve individual health and well-being. We believe innovation in sens-

ing is an important component to creating a means for appealing, usable, smarter digital health solutions.

DNA Medicine Institute (DMI) of Cambridge, Massachusetts, took home the grand prize of $525,000 for developing a portable device capable of running hundreds of clinical lab tests on a very small sample of blood. Results are available in a matter of minutes and are highly accurate. Five other teams—from Switzerland and England, and Illinois, Minnesota and California in the U.S.—also took home $120,000 each for their sensing innovations.

Our current life sciences prize is the Qualcomm Tricorder XPRIZE, a $10 million global competition to stimulate innovation and integration of precision diagnostic technologies, helping consumers make their own reliable health diagnoses anywhere, anytime.

Advances in fields such as artificial intelligence, wireless sensing, imaging diagnostics, lab-on-a-chip, and molecular biology will enable better choices as to when, where, and how individuals receive care, thus making healthcare more convenient, affordable, and accessible. We will award the team whose technology most accurately diagnoses a set of diseases independent of a healthcare professional or facility, and which provides the best consumer user experience with their device. In fact, we just recently down-selected to the top 7 teams from 4 countries—the United States, Taiwan, Canada, and India—who are currently in the process of testing.

With that said, understand that prizes don't work well across the entire healthcare spectrum owing to major barriers to entry, cost and time-intensity. So, where do we think they do work well?

- Where new forms of cross-disciplinary collaboration are needed;
- Where research is underfunded or there is a small patient pool driving inefficient market activity; and
- Where "engineering" type solutions could bring breakthroughs to bear.

Where prizes don't work well in healthcare (and where other programs should be continued):

- Early stage research/discovery; and
- Large, longitudinal research efforts which are too long for a prize (10+ year studies).

Even where we believe prizes work well, they can always complement traditional forms of funding, and should not be seen as a replacement for traditional forms of funding.

Currently, we are exploring additional prizes in organogenesis, kidney disease and Alzheimer's.

- *Organogenesis:* Nationwide, the supply of viable organs simply does not meet the growing demand. In 2012, 114,690 transplants were performed according to the World Health Organization's Global Observatory on Donation and Transplantation. This number of transplants represents only approximately 10 percent of the roughly one million organs needed worldwide. It also demonstrates stagnant growth from the numbers reported in 2008, largely due to a lack of growth in the number of available organs donated for transplant. XPRIZE is exploring a prize that challenges innovators to demonstrate the successful function of a bioengineered human tissue and/or human organ (heart, lung, liver or kidney).
- *Kidney Disease:* Kidney disease is caused by approximately 100 different diseases and disorders. Kidney disease treatment has seen little innovation in nearly 40 years. Investment and innovation is low and the market is dominated by large, for-profit dialysis providers that meet Medicare reimbursement standards. Significant research is needed to address those causes, but we do not develop XPRIZEs for basic research. This prize is designed to be a bridge between the current state of treatment (which is very expensive and has terrible outcomes for patients) and potential and/or the ability to grow new organs for transplantation. An XPRIZE will bring public awareness to the problem of kidney disease and the lack of innovation in treatment by focusing a community of innovators on key breakthroughs. Thus, XPRIZE is working in partnership with the American Society of Nephrology to develop and capitalize this prize.
- *Alzheimer's:* In partnership with 10 individual donors, we are exploring an Alzheimer's prize. While we are in the very early stages, we are seeking to improve diagnostics and effective treatments to alleviate symptoms of the disease. Senator Wicker has a keen interest in this issue and we have had very productive conversations with his staff about ways to encourage relevant agencies like NIH

and OSTP to support a prize around Alzheimer's. We applaud his leadership aimed at accelerating discovery and development of cures for Alzheimer's and related dementia.

The XPRIZE Prize Model

XPRIZE believes we can make the impossible possible by creating an infrastructure where our world's innovators create breakthroughs that both catalyze industries and have a measurable benefit to humanity. We do this via large-scale, incentive prize competitions.

Prizes are useful tools for solving problems for which the objective is clear, but the way to achieve it is not. By attracting diverse talent and a range of potential solutions, prizes draw out many possible solutions—many of them unexpected—and steer the effort in directions established experts may never take, but where the best solution may nonetheless lie.

Prizes are powerful for many reasons, the most important of which include leveraging your investment, democratizing innovation, and reducing risk.

Throughout the course of a competition, teams spend their own money to compete for the prize. We find that teams spend research and development dollars that, aggregated across all teams, is four to ten times the value of the prize purse. So, you could give a grant or contract worth $5 million and get $5 million worth of research and development, or you can put out a prize with a purse of $5 million and get upwards of $20 to $50 million worth. In a time of fiscal constraint, prizes are an extremely efficient tool to help spur innovation.

At XPRIZE we say, "Why find the needle in the haystack when that needle can find you?" Hosting a prize does just that. Prizes inspire teams from around the world to compete to achieve your goal—and often those that are inspired are not the current industry incumbents. Some solvers are from tangential fields and have a solution that could be tweaked to solve the challenge at hand, while others possess little to no experience at all. A prize does not care if someone has 20 years of experience or 20 days of experience—as long as they meet the goal of the competition. Using a traditional grant or contract, you would be very unlikely to find such innovators. Your focus would fall on the known players who comprise your target audience. Let me give you some examples. In the 1714 Longitude Prize—established by the British government to reward the precise determination of a ship's longitude—everyone assumed it would be a ship's captain or astronomer who would win. But it was a clockmaker. In the 1919 Orteig prize for the first person to fly between New York and Paris non-stop, everyone assumed the winner would be one of the aviation leaders. They all failed because they were too conservative in the design of their planes and how they flew. Instead, it was won by a relatively unknown, 25 year-old mail pilot, Charles Lindbergh. In our Progressive Insurance Automotive XPRIZE, we had a group of high school students surpass much of the competition. In our Wendy Schmidt Oil Cleanup XCHALLENGE, a tattoo artist made it into the finals. And although his team did not win, it still did better than the industry standard at that time. In fact, in that prize, four of the ten finalist teams were new to the industry. Most likely you would have never awarded a grant or contract to these innovators because (1) you would have seen it as too risky, (2) you never would have known they existed, and (3) they never knew they had an interest in solving the challenge prior to the prize. To get disruptive innovations, we need to democratize innovation—encouraging anyone, from anywhere, with any background, to help solve our grandest challenges.

Third, prizes reduce risk. What separates prizes from traditional R&D and other funding mechanisms is that the burden of risk is wholly on the teams, since the prize is designed only to reward success. That is, you only pay when a team meets your goal. In a traditional grant or contract, you would award it to the known players because that is less risky for you. But the known players want to be successful, so they are not going to take those risks that are necessary to result in a truly transformational breakthrough. Failure is a necessity of invention, because innovation must build upon unsuccessful attempts. Those competing for the prize are willing to embrace this risk because they have little to lose. As we say at XPRIZE, "The day before anything is a breakthrough, it's a crazy idea!"

As you can see, prizes are extremely powerful and should be one of the primary tools in any innovation toolkit.

But, for prizes to work well, you need to ensure they are designed well. I just spoke about passing the risk to the teams and paying only for success. That leads to the question of why teams compete for prizes. Many point to the prize purse—and that is true—but the prize purse is only one of the incentives for teams to compete. We have found the best prizes offer valuable operational incentives for teams

to compete. A prize purse is often not enough for teams to compete because teams know that only one or two or three of them will win the prize purse.

The teams are really competing for the end market—for the ability to go out into the marketplace and become a profitable company. As such, we have found that the best operational incentives align with helping teams prepare to win that market—these include incentives such as marketing, testing, milestone prizes, partnerships, and education.

A well-designed prize markets the prize, the teams, and the solutions. This allows the teams to show their progress and results to the world—including potential funders and customers.

Testing is key to incentivizing teams to compete. Often teams come out of our competitions with independent, third party verified data—data they can take to the marketplace to help raise funding or data that they can show to potential customers. Sometimes this testing costs us millions of dollars, but it is necessary to prove a winning solution works and has the added benefit of being extremely valuable to teams. For example, in our Adult Literacy XPRIZE, the top five finalists will have their solutions tested on 1,000 adult learners each over a 12-month period. Imagine a small startup doing this testing on its own, or even a large company. It would be very difficult, but the value of the data collected is enormous.

Milestone prizes are mid-way prizes that we offer during many of our competitions. They reward teams for certain successes along the way or reward those teams that make it through a down select. These are extremely valuable to teams insofar as they provide them with a small amount of funding to push forward and get press around their early wins. That press, again, helps them to raise funds and/or bring in potential customers.

Partnerships in terms of access to potential funders or investment funds, additional testing, advanced market commitments, and the like provide teams with other ways to market, test, and raise funds. We try to develop partnerships with organizations relevant to the prize area. I will focus on these partnerships more a bit later in this testimony.

We all know that sometimes the best innovators are not the best business people. Because the way to truly disrupt an industry or change the world through the prize is to get as many of the teams out in the market place with successful technologies—not just the winners—we believe that significant effort should be placed on educating the teams on how to formulate business plans, perform road shows to raise money, understand the regulatory impacts of their business, and other valuable business functions. Without this education, the prize may end up with good solutions, but the teams may not be able to commercialize the solutions.

In order to get the best results, we believe that you must provide additional incentives and value to the competing teams beyond the prize purse.

Prizes are One Way to Spark the Innovation Cycle

We strongly believe that the private and public sectors must work together to utilize every tool available to facilitate meaningful innovation that drives economic growth. Prizes are not a replacement for traditional financing mechanisms, but are augments to them. They are one of many innovation tools that agencies and the Federal Government should consider utilizing in tandem with other financial mechanisms such as grants, contracts, investments and incentives.

It is important to note that the resulting technology solutions are not replacements for behavioral change. Understanding how and where prizes work best will help ensure that they are used most efficiently and effectively. One of the hallmarks of an XPRIZE is its ability to create and/or catalyze industries. In this regard, the XPRIZE's impact does not begin at its launch, but with its award. Prizes, therefore, are the beginning, not the end, of the innovation cycle, maximizing the impact on emerging industries, scaling new ideas, and ultimately contributing to the economy.

Prizes provide a mechanism to discover breakthroughs that generate, operate and become part of the industrial base. They can catalyze an industry in order to have a real set of benefits for humanity. When an industry undergoes a catalyzing event as the result of a breakthrough, everyone benefits—humanity, industry, and the public perception of what's possible.

Importance of Policy to Send a Signal

The Federal Government has rightly recognized the power of prize competitions to draw out the latent innovative vision that simply hasn't found the means or the outlet to reach its potential. Following passage of the 2010 America COMPETES Act, which granted agencies the authority to operate prizes, and President Obama's "Strategy for American Innovation," which called on agencies to use Grand Challenges as an innovation tool, there has been an up-tick in the utilization of prizes

by the Federal Government. In 2015 alone, 30 agencies self-reported a total of 97 prize competitions and challenges. The prize opportunities ranged in value from as low as $2,500 to greater than $1 million, across industry sectors. These prizes have enabled government agencies to establish ambitious goals, pay only for success, and utilize novel approaches from outside partners to achieve their goals.

Now, Congress has an opportunity to once again use policy as a driver for innovation by passing the Science Prize Competitions Act—which passed the House of Representatives earlier this year. We look to the leadership of this subcommittee and the full Senate Commerce Committee to complement the bipartisan efforts of the House by introducing and passing policy supportive of prizes, much as it did in 2010 with the America COMPETES Act. We believe legislation that provides guidance to utilize high-impact prizes as an economically efficient way to incent innovation sends a strong signal to Federal agencies, and also to the private sector and innovation community, that the Federal Government believes in the power of prizes as a source of innovation.

The Value of Public-Private Partnerships

At the crossroads of policy-driven innovation and "garage ideas", I have witnessed remarkable breakthroughs brought about by critical partnerships between the public and private sector. For example, XPRIZE partnered with the Department of Energy to support a $10 million global competition to inspire a new generation of viable, safe, affordable, and super fuel-efficient vehicles. We brought together government and the private sector, including our lead sponsor Progressive Automotive Insurance. Our top prize-winner, Oliver Kuttner, a commercial real estate developer who loved to tinker with cars since taking auto shop in high school, maxed out his wife's credit cards to invest in chasing his dream—which culminated in his construction of a four-seat, 830-pound vehicle that ran on a one-cylinder, ethanol-fueled internal combustion engine that achieved 102.5 miles per gallon fuel efficiency. Today, Kuttner's company, Edison2, is continuing to develop extremely light, super fuel-efficient vehicles including an electric version. That is the kind of citizen innovation we take pride in fostering at XPRIZE.

Another ongoing example of government playing a supportive role even without supplying any financial support is the Qualcomm Tricorder XPRIZE. The U.S. Food and Drug Administration (FDA) is an integral partner in the effort, which XPRIZE is supporting with funding from our lead sponsor, the Qualcomm Foundation. In addition to assisting teams in preparing for future regulatory clearance post-competition, this prize competition is helping the FDA maximize its own readiness for new regulatory submissions in the direct-to-consumer diagnostics space.

Partnerships such as these have a history of maintaining a commitment to scientific excellence by guiding the conception, safety, and deployment for various technologies that have paved the way for the breakthroughs of today.

Conclusion

We strongly believe that the private and public sectors must work together to utilize every available tool to facilitate meaningful innovation that drives economic growth. As Congress explores ways to innovate in healthcare, prizes are one such essential tool that agencies, and the private sector, can, and should, consider.

Policymakers can encourage greater and more strategic use of prizes by agencies by supporting prize policy such as the House-passed "Science Prize Competitions Act". Passage would send a signal to agencies, the private sector and the innovation community that the Federal Government views the prize mechanism as an important solutions driver.

We look forward to continuing the dialogue with Congress about the power of prizes to unlock innovation towards finding cures for diseases, in addition to some the world's greatest challenges.

Senator CRUZ. Thank you, sir. Mr. Huber?

STATEMENT OF PETER W. HUBER, SENIOR FELLOW, MANHATTAN INSTITUTE

Mr. HUBER. Thank you, Chairman Cruz, for having me here today, and thank you also for your list of diseases you mentioned specifically in your opening remarks, and also the thousands and thousands of rare diseases. Senator Peters, you mentioned "what the next big thing is." The next big thing is already here.

I am quite confident we actually have today in hand the tools that will end up, and here the phrasing gets a little delicate. I would still call it "curing" but you would probably call it "preventing."

I think almost every disease you mentioned, Chairman Cruz, has a genetic origin of some kind. We are born with those diseases. We just don't see the symptoms until we are much older, but the genes that make it likely that they will develop are embedded in us, and we know what they are. We have gotten very good at tracking diseases back down to their origins.

In the last five years or so, we have also developed, not me personally, but we have developed a remarkable array of tools that let biochemists reach down into live cells and turn genes on or off or chop them out or embed a new one in there. These have been tested quite intensively in labs. They do work. We can actually go in and take away bad genes. We can replace them with sort of neutral genes or quite often other genes that make people extremely good controllers of disease-causing factors.

If you are born with the right genes, you will never develop high cholesterol because you have a feedback mechanism inside you that is based on a mutant of PCSK9, (I am sure that clarifies things), and it will keep your cholesterol levels low throughout your life. We know what it is. They have a drug now that simulates it as well.

We can go in there. We can take problem genes out. This is quite controversial. Many people think immediately oh, we are going to have designer babies and all sorts of abuses of these things, but we are not talking about that at all.

By the way, we also have, finally, the discovery of interfering RNAs by Philip Sharp, Nobelist at MIT, that has led to a whole new category of drugs, which do not involve the genetic engineering but they can be prescribed to turn genes on or off. If you have bad genes, at the very least, you can neutralize them.

Why are these treatments not out there already? They are out there in labs. They are being tested in clinical trials. This is not pure speculation by any means. I will jump to the end. If we want to get them out there fast, we should get the FDA to begin not generally approving their use by doctors, that would be much too fast, but getting them out to doctors who specialize in the treatments of these various disorders and have a lot of experience with struggling to cure the currently incurable.

We should get them out under "treatment IND" protocols which leave the doctors with broad flexibility to test out different options and try to understand and get early reads on whether these treatments are working, and we should get that data pooled. It should go into databases that begin to tell us which patient profiles are likely to respond well to these treatments, hopefully most of them, but it is almost never the case that a drug or anything else is 100 percent effective. There will always be some variations of patient chemistry out there that just do not let it work right.

These are serious treatments. You do not want to begin going in reprogramming people's bodies, unless you are pretty confident you have a high level of success, and we are going to get that only by letting doctors develop this stuff, gather the data, and get criteria which will let us predict which patients will respond well.

The FDA does not do that at all often. I think if we do that, if we unleash these tools to the right doctors and let them use them, they will be the first ones to know that this drug ought to be out there more generally available for doctors with somewhat less expertise than they bring to bear.

What I am describing falls somewhere between "adaptive trials," which the FDA has endorsed with lukewarm enthusiasm, and the "treatment INDs," which were mentioned by Dr. Coburn, the notion that yes, we can learn a lot by treating patients with stuff we have and learning as we go. The standard reason for not allowing that and requiring placebos and so on has always been doctors are subject to selection bias, they really hope it is going to work so they see success even when it is really failing.

I think that is a problem, a legitimate problem, but you know, there are plenty of very good high level centers where the doctors really are committed to getting things right and working on the new cures. We ought to trust them more than we currently do.

It will take quite some doing to get any of this accepted by the FDA, but we should be moving in that direction.

What would the doctors be learning that would not be learned in a standard FDA trial? Let's say I am going to go begin reprogramming somebody's body, which is what we are talking about, you begin asking yourself what do I reprogram, do I do this for the whole body, do I do it for stem cells, and then return them to the body and let them proliferate and sort of spread the wealth and so on.

We are talking here about a completely new kind of treatment. A gene is not a drug, right. You put a real good gene into somebody's body, it does absolutely nothing on its own. It has to rely on enzymes and adjacent genes. They work collaboratively. It is basically one set of instructions in a much larger program.

One hopes most of the time they will work just fine, you put in the gene, and everybody is pretty much the same everywhere else, but it probably won't work out that way. You have to begin looking systematically for the molecular criteria that will make such treatments work well. It is a procedural thing at the FDA. It is arcane. Most people's eyes glaze over on this, but we have to get these treatments out there.

I might add finally we are so certain about the genetic correlations in a number of these diseases that to my mind, and I am not a doctor and it is not for me to think these through for doctors, but I think it is beginning to border on the unethical if the FDA says sure, we have this genetic engineering system that may be—for example, I am taking it out of the blue but it is only because it is a much discussed example—if your daughter is born carrying two BRCA genes, she is probably going to get breast cancer once she is older. It is almost that certain. Not 100 percent certain but somewhere up there.

We know what the genes are. We can detect them an hour after she is born or we can wait 20 years later. Do we wait to post-puberty because there is no breast tissue to go cancerous before that?

These genes are going to be there from day one, so how soon do we go there? Do we have to fix cells all over the body? These are things that doctors think through, they try out, they explore. It

does not currently happen under any FDA protocols. We have to get doctors involved earlier in this business.

I am past my time. My apologies.

[The prepared statement of Mr. Huber follows:]

PREPARED STATEMENT OF PETER W. HUBER, SENIOR FELLOW, MANHATTAN INSTITUTE

The FDA's mission as set out in statutory language written over 50 years ago, is to see to it that drug companies generate and doctors receive on the FDA-approved label that accompanies ever drug, the information they need to prescribe the drug safely and effectively. For the most part, the agency continues to use drug trial protocols established in the 1960s, well before pharmacology developed the diagnostic and tools for designing precisely targeted drugs that make precision medicine possible.

The clearest evidence that the FDA has not kept up with the advances in the science and technology of precision medicine is that it is losing its grip on how drugs are prescribed. In steadily growing numbers, doctors that specialize in the treatment of complex diseases are taking the initiative, using the state-of-the art technologies and analytical tools to develop the science themselves, and relying on their own analyses and databases to guide the safe and effective prescription of drugs to their patients.

And that fact alone points to a serious problem. Doctors can't take the lead in working out how to prescribe a drug to the right patients until the drug has been approved. Which under the existing statutory language means that the drug first has to perform well in FDA-approved clinical trials. But to perform well in a clinical trial a drug has to be prescribed to the right patients.

It has become clear in recent years that traditional symptom-based definitions of diseases that are used to frame most clinical trials ignore what matters most in modern pharmacology—the same symptoms can be caused by a cluster of different molecular processes, and a precisely targeted drug can only control one them. A drug's efficacy and safety can also depend on a wide range of other molecular factors that are hard to identify in advance. We still speak of "developing a drug," but "developing the patients" would be more accurate. Both matter, of course—pharmacology isn't a science of one hand clapping—but all the complex biochemical details lie on the patients' side of the applause.

Oncologists have led the way in recognizing the limitations of the FDA's drug-approval process. In 2007, the Cancer Biomarkers Collaborative (CBC), a coalition of cancer experts drawn from the American Association for Cancer Research, the FDA, and the National Cancer Institute, started investigating the "growing imperative to modernize the drug development process by incorporating new techniques that can predict the safety and effectiveness of new drugs faster, with more certainty, and at lower cost." A summary of the conclusions published by the CBC in 2010 noted that "traditional population-based models of clinical trials used for drug approval are designed to guard against bias of selection, which may form the antithesis of personalized medicine, and accordingly, these trials expose large numbers of patients to drugs from which they may not benefit."

Other medical disciplines are following oncology's lead. Two years ago, for example, the National Institute of Mental Health (NIMH), the world's largest funder of mental health research, announced that it was "re-orienting its research" away from the disease categories defined by psychiatrists in their Diagnostic and Statistical Manual of Mental Disorders. Henceforth NIMH funded researchers will be encouraged to search for molecular pathways that transcend the symptom-based categories. In the words of the NIMH's director "patients and families should welcome this change as a first step towards 'precision medicine,' the movement that has transformed cancer diagnosis and treatment."

Other diseases are being analyzed in similar ways. The National Institutes of Health's Accelerating Medicines Partnership, recently announced a $230 million, five-year plan to collaborate with 10 big drug companies and eight non-profit organizations focusing on specific diseases, to unravel the molecular pathways that lead to Alzheimer's, Type 2 diabetes, rheumatoid arthritis, and lupus—and to investigate new methods to track a disease's progress that could provide early reads on how a drug is affecting it. The objective is to "ensure we expedite translation of scientific knowledge into next generation therapies." A Pfizer representative emphasized that the Alzheimer's project will focus on developing a better understanding of the molecular pathways and networks that propel the disease. It will also include searches for molecular factors that can be used to develop drugs that intervene much earlier, intercepting diseases before they become irreversible and untreatable.

The advent of tools to unravel the molecular pathways of diseases, and drugs precisely designed to target them have called into question the conventional symptom-based medical taxonomy of diseases, and thus, indirectly, the central role it still plays at the FDA. In 2011, a task force convened by the National Research Council (NRC) released *Toward Precision Medicine,* a report written at the request of the NIH to address the need for "a 'New Taxonomy' of human diseases based on molecular biology." We do indeed need one, the report concludes, and to facilitate its development, the report recommends the creation of a broadly accessible "Knowledge Network" that will aggregate data spanning all molecular, clinical, and environmental factors that can affect our health. Working out the molecular etiology of complex diseases will require an analysis of "biological and other relevant clinical data derived from large and ethnically diverse populations" in a dynamic, learn-as-you-go collaboration among biochemists, clinical specialists, patients, and others.

The report also includes an illustration of how we currently rely on dumb luck to help drugs that target complex disorders stumble their way through the FDA's testing protocols. In 2003 and 2004 the FDA granted accelerated approval to two drugs, Iressa and Tarceva, on the strength of their dramatic therapeutic effects in about one in ten non-small-cell lung cancer patients. Over the course of the next two years the drugs were prescribed to many patients whom they didn't help, and several follow-up clinical trials seemed to indicate that the drugs didn't work after all—probably, we now know, "because the actual responders represented too small a proportion of the patients." Meanwhile, the report continues, the molecular disassembly of lung cancer had begun its explosive advance. In 2004, researchers identified the specific genetic mutation that activates the EGFR enzyme that these two drugs inhibit. "This led to the design of much more effective clinical trials as well as reduced treatment costs and increased treatment effectiveness." Under current, blinded trial protocols, however, such launches often depend on luck and circular science. The original clinical trial happens to include just enough of the right patients to persuade the FDA to license the drug. The fortuitously and just barely successful completion of the first clinical trial then starts the process that may ultimately supply the information that, ideally, would have been used to select the patients to include in that first trial.

In early 2005 Iressa became the first cancer drug to be withdrawn from the U.S. market after the required follow-up trials failed to confirm its worth to the FDA's satisfaction. After further trials failed to establish that Iressa extends average patient survival, and serious side effects surfaced in some patients, the manufacturer halted further testing in the United States.

We do however, know that Iressa survival times and side effects vary widely among patients. And we have a pretty good idea why. As Bruce Johnson, a researcher at Boston's Dana-Farber Cancer Institute and one of the doctors involved in the original Iressa trials, remarked in 2005, "For us as investigators, at this point, there are at least 20 different mutations in the EGF receptors in human lung cancers, and we don't know if the same drug works as well for every mutation . . . which is why we want as many EGFR inhibitor drugs available as possible for testing."

When the FDA rescinded Iressa's license, it allowed U.S. patients already benefiting from its use to continue using it. One such patient who started on Iressa in 2004, when he had been given two to three months to live, was still alive eight years later, and walking his dogs several miles daily. Rare cases like his have no influence at the FDA but are of great interest to doctors and researchers. In 2013, the National Cancer Institute (NCI) announced its Exceptional Responders Initiative. Four major research institutions are analyzing tissue samples, collected during clinical trials of drugs that failed to win FDA approval, to identify biomarkers that distinguished the minority of patients who did respond well from the majority who did not. The analysis of roughly a decade of prior trials in the first year of the study identified about 100 exceptional responders. As of March 2015, more than 70 cases have been provisionally accepted for further analysis, with hundreds more anticipated. Accepted tumor tissue samples "will undergo whole-exome, RNA, and targeted deep sequencing to identify potential molecular features that may have accounted for the response." When the molecules that distinguish the exceptional responders align with what the drug was designed to target, these findings could well lead to the resurrection of drugs that might have helped many patients over the last decade.

In one such trial the drug failed to help over 90 percent of the bladder cancer patients to whom it was prescribed. But it did wipe out the cancer in one 73-year old patient. A genetic analysis of her entire tumor revealed a rare mutation that made her cancer sensitive to the molecular pathway that the drug modulates. Similar mutations were found in about 8 percent of the patients, and the presence of the

mutation correlated well with the cancer's sensitivity to the drug. Similar analyses of a decade of other trials have identified about 100 exceptional responders and could well lead to the reexamination and approval of drugs that could have started saving many lives years ago.

Which brings us back to why doctors who specialize in treating complex diseases are increasingly confident that they should work out how to practice precision medicine independently, without relying on FDA-approved labels. In brief, it comes down two things. Researchers have developed the tools needed to work out the details of how molecular processes that go wrong deep inside our bodies spawn and propel diseases. And drug designers have developed a remarkable array of tools to design precisely targeted drugs that can disable or control those pathways.

New devices now make it quite easy to collect large amounts of genetic and other medically relevant data from many people. Amazon and Google are reportedly in a race to build the largest medically focused genomic databases. According to Google's genomic director of engineering, Google aims to provide the best "analytic tools [that] can fish out genetic gold—a drug target, say, or a DNA variant that strongly predicts disease risk—from a sea of data." Academic and pharmaceutical research projects are currently the company's biggest customers, but Google expects them to be overtaken by clinical applications in the next decade, with doctors using the services regularly "to understand how a patient's genetic profile affects his risk of various diseases or his likely response to medication."

Medicine will also benefit from the fact that the statistical tools needed to unravel causal pathways from complex datasets are of great interest in other sectors of the economy as well. The "overarching goal" of the "Big Mechanism" program recently launched by the Defense Department's Advanced Research Project Agency (DARPA) is to develop methods to extract "causal models" from large, complex datasets and integrate new research findings "more or less immediately . . . into causal explanatory models of unprecedented completeness and consistency." To test these new technologies DARPA has chosen to focus initially on "cancer biology with an emphasis on signaling pathways." It's a good call, and excellent news for oncology. Viewed from a data analytics perspective, the variability, complexity, and adaptability of cancer cells and terrorists have much in common.

Drug companies rely on our ability to expose disease-causing molecular chain reactions to identify key targets that if disabled or controlled by drugs will cure the disease. The tools currently used to design precisely targeted drugs have been widely used in developing effective later stage treatments and clearly have the potential to identify and take control of the factors that launch diseases at the outset. Many serious disorders develop slowly however, and there is little doubt that successful interventions at a very early stage will often be the best, sometimes the only, and almost always the most cost-effective way to beat them. The development of effective cures will depend on tracing their causes back to their molecular origins and addressing the root causes of the disease rather than attempting to treat the symptoms that surface much later.

The tracing is already is already well underway. We know that the genetic seeds of many disorders are planted at the time of conception and lie dormant inside our bodies for many years before they start morphing into lethal diseases. An array of tumor suppression and DNA repair genes, for example, protect most of us from cancer for most of our lives. Hereditary variations in those genes affect how well they perform, and some are strongly linked to the development of specific cancers—breast, skin, or colon cancer, for example—or, in some rare cases, a propensity to develop cancers throughout the body.

Now emerging are gene therapies that offer a broad range of radically new medical interventions. Researchers have recently mastered powerful and flexible methods for selectively adding, deleting, or replacing genes in a live cell's genome. These tools can do in weeks what often required months or years of work using previous gene editing tools. And a new family of "RNA interference" drugs have the potential to regulate gene expression and thus take direct control of genes involved in the earliest stages of disease development. Most gene therapies are still in the investigational stages of development. But their feasibility and great promise is no longer in doubt. And no other currently known process has the potential to provide complete cures for the many rare but often deadly disorders caused by hereditary genetic mutations.

The next step could well be vaccine-like treatments that provide protection before cancers and other disorders start to develop. Researchers are investigating a number of different vectors for reprogramming the genetic code of cells inside a patient's mature tissues and organs. In early trials, for example, young adults blinded by a rare genetic flaw experienced significant visual improvements soon after a viral vector was used to insert a healthy version of the gene directly into their retinal cells.

Similar procedures are reportedly being developed to treat cystic fibrosis, brain cancer, and muscular dystrophy.

Genetic therapies administered early enough to replace pathological variations in gene repair and tumor suppression genes could offer many people a significant, lifelong reduction in their risk of succumbing to what is currently the second most common cause of death in the United States. Rare variations in a single gene make some people prone to develop very high levels of cholesterol and suffer heart attacks in their teens. A more common variation in the gene has the opposite effect, and researchers are investigating the possibility of reprogramming cells to replace the high cholesterol versions of the gene with the low-cholesterol versions. The HIV retrovirus pries its way into our immune system cells by latching one of two proteins on the cells' surfaces. A recent trial demonstrated the therapeutic potential of genetically engineering a patient's own immune-system stem cells to replace or disable the gene that codes for the HIV-entry protein. In the words of one of the doctors involved in the trial "This study shows that we can safely and effectively engineer an HIV patient's own T cells to mimic a naturally occurring resistance to the virus, infuse those engineered cells, have them persist in the body, and potentially keep viral loads at bay without the use of drugs."

While NIH researchers, doctors, and drug companies have demonstrated their confidence in relying on the analysis of the disease-causing molecular pathways when designing drugs and prescribing them to patients, the FDA has made clear that it will almost never approve a new drug on basis of a clinical demonstration that the drug can take shut down or repair a pathway. The FDA asserts—correctly—that a drug's demonstrated effect on a single, disease-specific molecular pathway often fails to predict its ultimate clinical effect on patient health.

But much of the time we already know why, or can find out if we wish to. However precisely targeted it may be, a drug's overall impact will almost always also depend on how it interacts with other parts of the patient' body. How the drug is metabolized by the liver, tolerated by immune system, or interacts with other parts of the patient's body to cause side effects can affect the drug's overall performance. Cancer cells and HIV virion mutate rapidly, so the disease itself keeps changing and effective treatment will then required more than drug prescribe to track the changes. Factors like these however, are at least equally likely to undermine predictions made by the FDA-approved label when its contents are based on what was learned in a conventional clinical trial.

The only way to work out how most of such factors affect a drug's performance is by prescribing it to a wide variety of patients and analyzing how differences in patient chemistry affect is safety and efficacy. In a tacit admission of the limits of its own trial protocols, the FDA itself helped launch a nonprofit consortium of drug companies, government agencies, and academic institutions to compile a global database of "rare adverse events" caused by drugs and link them to the genetic factors in the patients involved.

The need to involve doctors and patients in the process of developing precision prescription protocols was also recognized in a 2012 report "on Propelling Innovation In Drug Discovery, Development, and Evaluation" written by the President's Council of Advisors on Science and Technology (PCAST). "Most trials. . .imperfectly represent and capture. . .the full diversity of patients with a disease or the full diversity of treatment results. Integrating clinical trial research into clinical care through innovative trial designs may provide important information about how specific drugs work in specific patients."

The British government appears to have reached similar conclusion. It recently announced plans to integrate clinical treatment into drug-development efforts on a national scale. As described by life-sciences minister George Freeman,"our hospitals will become more important in the research ecosystem. From being the adopters, purchasers, and users of late-stage drugs, our hospital we see as being a fundamental part of the development process." Britain's National Health Service will become "a partner in innovative testing, proving and adopting new drugs and devices in research studies with real patients." While the details have not yet been made clear, the *Times* of London reports that "Ministers want to bypass traditional clinical trials by using patients as a 'test bed' for promising new drugs, linking [national] health service data to pharmaceutical company records to discover much more quickly how effective treatments are. Firms would be paid different prices depending on how well drugs work for individual patients. . . . Ministers argue that the system of assessing new treatments is no longer up to the job and that the National Institute for Health Care Excellence needs to catch up."

U.S. oncologists are already engaged in "rapid learning health care," a term coined in 2007 by a group of health care experts convened by the Institute of Medicine. In brief, the workshop participants proposed a process for continuously improv-

ing drug science using data collected by doctors in the course of treating their patients, with a particular focus on groups of patients not usually included in drug-approval clinical trials. By 2008, as discussed in a recently published paper authored by two experts in the field, several major cancer centers had established networks for pooling and analyzing data collected by doctors in their regions. These systems are being used to identify new biomarkers, analyze multidrug therapies, conduct comparative effectiveness studies, recruit patients for clinical trials, and guide treatments. Several commercial vendors now offer precision oncology services.

As discussed in the same paper, the powerful analytical tools and protocols now available, or under development, can use data networks to recommend treatments that would "avoid unnecessary replication of either positive or negative experiments . . . [and] maximize the amount of information obtained from every encounter" and thus allow every treatment to become "a probe that simultaneously treats the patient and provides an opportunity to validate and refine the models on which the treatment decisions are based." Analytical engines like these take statistical analysis far beyond the one-dimensional correlations traditionally relied on by the FDA in the drug-approval process, and thus lead to far more precise prescription of the drug in question.

The FDA does have in place a regulatory framework—"treatment IND"—that could be used to integrate clinical trial research with clinical care called the.

It was originally developed to provide unapproved drugs to AIDS patients in the early years of medicine's struggle with HIV. The original plan was that treatment-INDs would be used for more comprehensive investigation. In the late 1980s the National Institute of Allergy and Infectious Diseases (NIAID) began funding "community-based AIDS research"—studies of not-yet-licensed drugs in doctors' offices, clinics, community hospitals, drug addiction treatment centers, and other primary care settings. The treatment-IND framework remains available to provide investigational drugs to patients for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. This is done, however, only when the drug is already under investigation or standard trials have been completed, and the FDA has concluded that enough data has been collected to show that the drug "may be effective" and does not present "unreasonable risks." The drugs are provided for treatment but doctors also collect safety and side effect data.

More recently, the FDA established a "Group C" treatment IND was established by agreement between with the National Cancer Institute (NCI). The program allows the NCI to distribute investigational drugs to oncologists for the treatment of cancer under protocols different from those underway in under the FDA-approved protocols. Treatment is the primary objective, though here again safety and efficacy data are collected. The FDA usually authorizes Group C treatments only when the drugs have reached Phase III of standard clinical trials and have "have shown evidence of relative and reproducible efficacy in a specific tumor type."

A third FDA-approved initiative has also tiptoed toward integrating clinical trial research into clinical care. Sponsored by the Biomarkers Consortium, a partnership led by the Foundation for the National Institutes of Health (FNIH), which includes representatives of the FDA and the NIH), are investigating up to twelve different breast cancer drugs simultaneously in the I–SPY 2 trial. Patients are initially treated with the drug that targets the pathway that is propelling their cancer, but the trial uses adaptive protocols that allow the doctors involved in the research to use data from obtained from patients early in the trial to guide which treatments should be used for patients who enter the trial later. The data are fed into an analytical engine as soon as they are collected, and immediately verified and shared with participants. Drugs may be abandoned if they perform badly and other new drugs may be added. And the sponsor say that this is just a beginning that "holds tremendous promise for many cancers and diseases in addition to breast cancer" and also may lead to adaptive treatments within patients as new, successful drug-patient molecular pairs are identified.

These are steps in the right direction that, as the FDA asserts, will accelerate the drug approval process, reduce its cost, and substantially increase the likelihood that by improving prescription protocols during the trials more drugs will end up being approved. But all of three initiatives continue to require trials that continue long enough to demonstrate clinical efficacy. Even though it is becoming clear that we have the tools to work out disease molecular pathways correctly. Doctors confirm this every time they match a drug's mechanism of action to a pathway that is known be active a patient to successfully prescribe the drug off-label. By refusing to accept evidence that a drug can disrupt a pathway as sufficient evidence that the drug will have desired clinical effects the FDA is, in effect, requiring a demonstration that the pathway does indeed cause the disease. But that can be established independently, and often is, before the drug is designed. New drugs could be ap-

proved even faster and at still lower cost if the FDA would accept that body research as sufficient proof that proof that pathway disruption is proof of efficacy.

Experience has also already established that data collected by unblinded doctors during the course of treating their patients can be used to create databases that can be successfully used to guide drug prescriptions going forward. The approval of a targeted drug to treat a specific disease is, in effect approval of the drug's ability to target a pathway that propels the disease and thus approval of the science that led to the development of the drug by linking the two.

The FDA could and should go further, at least when dealing with new drugs that target serious, life threatening diseases that are currently untreatable.

Following threshold screening for toxicity and an early demonstration in what could be a small clinical trial that the drug can indeed disrupt the pathway that it was designed to target, the drug will, at the sponsor's request, be made available to selected centers that specialize in treating the disorder in question. The treatment protocols adopted by its doctors will be monitored by independent outsiders, at the FDA itself or designated by the agency, or by perhaps by one of the NIH institutes that sponsors research addressing diseases of that type. The doctors involved in the integration of clinical trial research and clinical treatment will work unblinded and without placebos, and be given broad discretion to adjust treatments, collect data, and analyze responses, as they do. The molecular pathway that propels the disease is important but there are usually other pathways that that also interact with the drug to cause side effects or in other ways that affect clinical outcomes, and many of them can't be identified without prescribing the drug to patients and analyzing why patient responses differ. And if one accepts—as many doctors do—that the biological science has reached the point where it can be trusted to predict clinical benefits on the basis of a drug's pathway-disrupting effects, doctors will have to start considering whether it is even ethical to conduct blinded placebo-controlled trials of a new drug that has already demonstrated its ability to have those effects to the doctors' satisfaction. Studies have also established that patients are much more willing to participate in trials if they are assured of being treated with a drug, not a placebo. And this approach will also address the increasingly vocal "right to try" demands from patients suffering from serious diseases and who desperately want immediate access to any drug that might help.

As is standard procedure in conventional trials the doctors will monitor for side effects and the overseeing authority would have the authority to halt use of the drug in response. The doctors will also use any available tools that can track the drug's effects on the progress of the disease, among them intermediate end points based on what is known about the normal rate of progression of the disease when left untreated. All data from all treatment centers will be pooled and all doctors will have access to the data and the continuously updated analyses of the data and use them to guide prescriptions going forward. If there is no good way to assess the drug's efficacy other than to continue the trial as long as a conventional trial would continue, and wait for clinical effects to surface or not surface that is what is what will be done. If doctors are, instead, able to demonstrate that steadily improving prescription protocols are steadily reducing the likelihood that the disease will steadily progress the doctors themselves will take charge of notifying the FDA when, in their view, more patients should be accepted for investigative treatment with the drug by more doctors at more treatment centers. If rate of positive outcomes continues to rise, at some point the FDA, again advised by the doctors who have been treating the patients could approve the drug for general distribution. But as medical records go digital, the more likely and better approach in the longer term will be to continue to track and analyze how patients respond to the drug indefinitely into the future, and continue refining prescription protocols for as long as the drug remains on the market. New side effects often surface as much as a decade after a drug is approved, and human bodies get reconfigured every time a new child is conceived.

It is worth noting, finally that there are times when relying entirely on a drug's molecular effects to demonstrate efficacy is indispensable: insisting on the use of clinical endpoints in conventional trials will only ensure that no treatment gets developed and approved. Requiring clinical endpoints means conducting trials that can't be completed any faster than diseases typically progress to the point where they cause clinical symptoms—and will take even longer than that when preventive drugs are designed to intervene before the diseases start to develop. The trials are very expensive, and the clock of drug patents keeps ticking while trials are conducted. . . . A 2006 article in the *New England Journal of Medicine* attributed the complete absence of drugs that would prevent, rather than just alleviate, the late-stage symptoms of diseases such as Alzheimer's or osteoarthritis to a drug approval process that "makes it hard, if not impossible" to move the drug through Washington before its patent expires. "[D]espite considerable advances in our under-

standing of such diseases, there is no validated and tested path to successful FDA approval of a drug to prevent these conditions. This lack of a clear plan for drug approval adds high regulatory risk to the already high scientific risk of failure."

Conventional clinical endpoints also present a more fundamental, if rarely noted, problem. Chronic diseases can cause irreversible effects, but when no treatment is available, there is little incentive to diagnose the disease early, so it usually is not diagnosed until clinical effects surface. At that point, a drug may be able to deliver so little clinical improvement to most patients that it is viewed as a failure.

Very rare diseases present another problem: there are often too few patients to conduct a statistically robust double-blind trial, and focusing on molecular scale effects is the only alternative. Moreover, rare hereditary diseases are often strongly and unequivocally linked to specific genetic mutations and the flawed proteins that they code for, and a drug's ability to block the protein's pathological effects or a genetic therapy's ability to replace the mutant gene with a normal one should be accepted as a concomitantly strong demonstration of the therapy's efficacy. This will be particularly important when dealing with genetic therapies. Because they are genetic, the disorders can start developing very early in life, and to be effective the genetic therapies will have to start equally early. But these disorders are usually slow to develop—if they very quick killers, the faulty genes probably wouldn't have lasted in the human gene pool for long. So to meet standard FDA requirements of demonstrated clinical benefits, groups of patients who receive these treatments might have to be monitored for many decades. Few drug companies will be eager to invest in these treatments if that is how long they are likely to have to wait for a return.

As Dr. Janet Woodcock, currently the head of the FDA's Center for Drug Evaluation and Research, noted over a decade ago, molecular biomarkers "are the foundation of evidence based medicine—who should be treated, how and with what.. . .. Outcomes happen to people, not populations." Precision medicine is inherently personal. The treating doctor and the patient are the only ones who have direct access to the information required to prescribe drugs with molecular precision. We will greatly accelerate, improve, and lower the cost of the drug-approval process by relying much more heavily on doctors who specialize in the treatment of complex diseases.

Senator CRUZ. Thank you very much, Mr. Huber. Dr. Yamamoto?

STATEMENT OF DR. KEITH R. YAMAMOTO, VICE CHANCELLOR FOR RESEARCH, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO; EXECUTIVE VICE DEAN, SCHOOL OF MEDICINE; PROFESSOR, CELLULAR AND MOLECULAR PHARMACOLOGY

Mr. YAMAMOTO. Good morning, Chairman Cruz, Ranking Member Peters, and distinguished members of the Subcommittee. I am Keith Yamamoto, Vice Chancellor for Research at the University of California, San Francisco.

I am honored to discuss with you today the impact of innovative biomedical research and precision medicine on preventing and curing disease and the role of Federal investment, policy, and regulation in enabling those advances.

Precision medicine is a new concept that will collect and analyze vast amounts of basic research and patient data using computational tools to build a network of knowledge that allows effective diagnosis and treatment decisions or provides disease prevention advice tailored to individual patients.

Why the need for all these data? Because we humans sense and respond to countless signals, internal ones like elation or anxiety, external signals like viral infection or a glass of fine wine, and each individual's responses to unique combinations of signals uniquely affects his or her health and likelihood of disease.

Precision medicine is like Google Maps, where the full picture is derived from stacking together many layers of different types of information, but instead of topology and roads and gas stations, it is

DNA sequence and blood glucose, blood levels, and exposure to secondhand smoke while growing up.

Together, many layers of data gathered from many people and from laboratory experiments produce a knowledge network, an increasingly precise picture of human health and disease.

The good news is that the network need not be complete to produce useful results, adding a single new data layer to those traditionally used to inform a therapeutic decision, for example, can have a tremendous impact. The progressive merging of small insights begins to reveal the full picture.

At UCSF, many precision medicine project pilots are underway, most of them in collaboration with industry, startup's, national labs, or other universities. These are underway across our whole research endeavor, basic, clinical, social/behavioral research, and our emerging knowledge network already has begun to impact our research, our health support, and our treatment of disease.

Projects around the country as well as at UCSF defining what it will take—what the needs are—for precision medicine to succeed, to unlock the cures for America's deadliest diseases.

Let me mention just four such needs. First, expanded and sustained support for fundamental discovery, that is, basic research. New discoveries remain essential both to define biological processes and to develop powerful new research tools, as Dr. Huber mentioned.

For example, after examining the genomes of bacteria that grow in a toxic superfund clean up site, brilliant basic scientists created an astonishing technology called "CRISPR/Cas9," which rapidly and economically allows any precise change to be introduced into the DNA of any living cell, potentially enabling, for example, the repair of disease causing mutations, increased crop growth or nutrient content, neutralization of disease carrying insects, and much, much more.

Only government agencies such as NIH, NSF, DOE, and DARPA can support the research that produces fundamental discoveries. Those Federal investments empower private sector developments. Understanding a disease mechanism, for example, can direct the design of drug candidates, define the structure and endpoints of clinical trials, limit the composition and size of trial cohorts, and shorten the duration of trials.

Each of these steps reduces costs and increases the likelihood of success. In fact, it really goes further than that. Drug companies approaching Phase III trials, the most costly and demanding of the FDA-mandated series of tests, have already invested hundreds of millions of dollars and need to make a decision on the probability that their drug candidate will succeed in Phase III. Knowledge of the mechanisms can inform their stratification of patient groups, thus reducing the size and length of trials, and increasing their success rates.

The fact is that many trials simply do not get done, that drug companies made business decisions, for lack of scientific understanding, not to carry out the trials. The chance of having a drug evaporates at that point.

Number two, transdisciplinary research. Precision medicine requires the concepts and tools of physics, chemistry, engineering,

and computer science, integrated programs such as those envisioned by OSTP, crossing the boundaries of NSF, NIH, FDA, DOE, DARPA, and NIST, and partnering with industry are crucial. Research programs sponsored jointly by two or more agencies can spur the types of discovery and tool building that are needed.

Number three, big data, interoperable data sharing, computational learning, and data security. New technologies for analysis massive sets of diverse data types, at scales that necessitate efficient and secure data sharing, will be developed in partnerships between Federal agencies, national labs, and private industry. Some of that work is well on its way.

Thus, these capabilities will require that patients and well people agree to provide and share data, a willingness that in turn requires government policies that address privacy, security, ethical, legal, and social issues.

Number four, regulatory science and regulatory policies. NIH, NSF, NIST, and especially FDA, recognize deep needs for science based regulatory technologies and methodologies to accelerate clinical trials, enhance post-market vigilance, and create standards for genome sequencing, novel trial design, cell based therapies, and risk/benefit assessments of devices and therapies. In fact, a lot of new programs are underway or planned at the FDA to address these needs, and deserve to be recognized.

A national precision medicine knowledge network deserves Federal support with its promise to improve health and prevent disease, and unlock cures for America's deadliest diseases.

If precision medicine fulfills its promise for a healthier and more productive workforce, better control of chronic disease, smaller and more successful clinical trials, and avoidance of unnecessary tests and ineffective therapies, the slope of the currently unsustainable health care cost curve could decline.

Thus, precision medicine holds the potential to produce broad positive outcomes for science, for society, and for the economy.

Thank you, Mr. Chairman. This concludes my testimony. I would be happy to respond to questions.

[The prepared statement of Mr. Yamamoto follows:]

PREPARED STATEMENT OF DR. KEITH R. YAMAMOTO, VICE CHANCELLOR FOR RESEARCH, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO; EXECUTIVE VICE DEAN, SCHOOL OF MEDICINE; PROFESSOR, CELLULAR AND MOLECULAR PHARMACOLOGY

Good morning Chairman Cruz, Ranking Member Peters and distinguished members of the Subcommittee, I am Keith Yamamoto, Vice Chancellor for Research at the University of California, San Francisco; I serve also on the Advisory Committee of the Division of Earth and Life Studies for the National Academy of Sciences, on the Advisory Council of the National Academy of Medicine, on the Board of Directors of Research!America, and chair the Coalition for the Life Sciences. I am pleased to provide this testimony for the record.

It is an honor to appear before you today to discuss public-and private sector efforts in biomedical research innovation and precision medicine, and their impact on preventing and curing disease.

It is an especially opportune time for this discussion. A confluence of the physical, technological and health sciences has created the opportunity for a transformational leap forward—a revolutionary change in biomedical research, health and healthcare. Thoughtful and timely Federal investment, policy and regulation will be essential and critical drivers of these advances.

Precision medicine[2] is a major new concept that will collect, integrate and analyze comprehensive data across basic research and massive patient cohorts, creating an interactive network of knowledge that allows effective, mechanism-based diagnosis

and treatment decisions for each individual patient, while at the same time empowering further research and advancing clinical care. It differs dramatically both from *current medical practice,* in which diagnosis and treatment decisions are based on a patients medical history and analysis of her/his presented symptoms, and from *personalized medicine,* which improves diagnosis and treatment decisions by collecting more detailed information about the individual, but does not integrate discoveries from basic science or information from other patients.

Why is it important to do precision medicine? Because we humans are complicated—and for good reasons. Rather than being hardwired by our DNA, we sense and respond to internal (*e.g.,* hunger, anxiety) and external (*e.g.,* infection, environmental exposures) signals, and the combined output of hundreds of complex contributing factors and interactions influences our individual health status as well as the onset and course of any disease. Thus, a defining assertion of precision medicine is that our genomes, our individual DNA sequences, are powerful determinants, but in no way provide enough information to understand or predict human physiology and human disease. Myriad other components—molecular, developmental, physiological, social, and environmental—also must be monitored, aligned, and integrated to arrive at a meaningfully precise and actionable understanding of disease mechanisms and of an individual's state of health and disease. The 2011 U.S. National Academy of Sciences (NAS) report entitled *Toward precision medicine: Building a knowledge network for biomedical research* used the analogy of Google maps to illustrate the value and necessity of aligning and integrating diverse, often unstructured, data sets into a comprehensive knowledge network if we are to understand the complexities of human health and disease.

Thus, precision medicine is not a new field of study or a subspecialty but rather an approach to acquiring knowledge that integrates across the spectrum of biomedical research and clinical practice; it is a platform for organizing, synthesizing, and rationalizing information in ways that change fundamentally how we conduct biomedical research and care for patients. The success of this approach will depend on the engagement of wide stakeholder communities, basic and social scientists, clinicians, patients and healthy people, pharma and high-tech industry, payers, and of course the Federal Government.

President Obama's Precision Medicine Initiative gives voice to this complex task, with his call to create a million-citizen cohort to contribute and share their health data while maintaining privacy and security. Similarly, California governor Jerry Brown has created the California Initiative to Advance Precision Medicine, providing funding to motivate public-and private-sector teams to collaborate and to contribute resources.

Clearly, the precision medicine effort is massive and daunting in scale, demanding sustained effort likely to be measured in decades. But here's the good news: efforts already underway demonstrate that the knowledge network need not be *complete* to produce *success.* Adding a single new data layer to those traditionally used to interrogate a disease mechanism or inform a therapeutic decision can have substantial impact. And the progressive merging of small insights will begin to reveal the full image. At UCSF, where precision medicine is central to our institutional strategy and vision, various pilot projects, most of them collaborations with industry, startups, national labs or other universities, are underway across basic, clinical, and social/behavioral discovery research, and our knowledge network, initially rooted in cancer and neurological disease, is spreading to include other disciplines and disease areas. Our still-early efforts are already impacting our basic research, our understanding and support of human health and our treatment of disease.

In addition, from pilot projects at many institutions across the country, we are gaining a sharper focus on what it will take for precision medicine to truly succeed. As these needs align strikingly with the focus of today's proceedings, I shall enumerate several of the most compelling, with particular emphasis on critical investment, policy and regulatory instruments from congress and Federal agencies.

E*xpanded, sustained support for basic research.* Despite remarkable progress, our understanding of biological principles and processes remains rudimentary, and it is certain that learning the fundamentals is essential for establishing the basis for disease, the features that make disease proceed differently in different individuals, and for development of new technologies that produce progress in leaps rather than steps. For example, reading the genomes of bacteria that thrive in the harsh environment of a SuperFund cleanup site has created, in the hands of brilliant basic scientists, "CRISPR/Cas9 technology", which simply, rapidly and economically allows precise changes to be introduced into the DNA of any living cell—potentially enabling repair of disease causing mutations, increased crop growth or nutrient content, neutralization of disease carrying insects, and much much more.

Only the Federal Government, *e.g.,* NIH, NSF, DOE, DARPA, can support basic research at the level and scale needed to produce a flow of fundamental discovery. By contrast, the private sector must maintain tight foci on mission-oriented goals. The Federal investment then empowers development and application by the private sector. In precision medicine, the public and private efforts can increasingly be productively linked. Knowledge of a disease mechanism, for example, can motivate the design of drug candidates, define the structure and endpoints of clinical trials, tightly stratify and reduce the size of trial cohorts, and shorten the duration of trials. Each of these steps reduces the cost of drug development while increasing the likelihood of successful outcomes.

Transdisciplinary research. As a quantitative endeavor, precision medicine must power its biological inquiry with the concepts, tools and methodologies of physics, chemistry, engineering and computer science. Integrated programs, funded across agency lines (*e.g.,* NSF, NIH, FDA, DOE, DARPA, NIST) such as those envisioned and effectively promoted by OSTP, will be increasingly essential and impactful.

Big data, data sharing, computational deep learning, data security. A computational challenge to devise technologies for acquisition, integration and analysis of massive sets of diverse data types must be met by research supported by Federal agencies, national labs and private industry. With those capabilities must come establishment and embrace of a new social contract by patients and well people, a willingness to provide and share data underwritten by policies that address privacy, security, ethical, legal and social issues. Cooperative science and policymaking efforts across funding and regulatory agencies, and likely legislative action as well, are essential here.

Standards and regulatory guidance, interoperability of data sensing and reporting devices and records. Efforts toward standardization and interoperability are beginning with management of genomic data and integration with electronic health records, but the challenges are broad and deep. Device builders in the private sector will be motivated by clear regulatory guidance. Cooperative scientific and policy efforts across FDA, NSF, NIST are essential.

Regulatory science and regulatory policies responsive to precision medicine needs and opportunities. There are deep needs for science-based regulatory technologies and methodologies. NIH, NSF, NIST, and especially FDA recognize and have begun to address a range of challenges, including accelerating clinical trials, enhancing post-market vigilance, and creation of science-based standards for next generation sequencing, novel trial design, cell-based therapies, predictive toxicology, risk:benefit assessment for devices and therapeutics, and validation of generic drugs. Those efforts, within and across those agencies, merit increased support.

Precision medicine is envisioned as a national or international enterprise, an audacious aspiration to be sure. However, success in much smaller increments is demonstrating how insights gained from integrating many data elements will advance us, through modeling, and testing of predictions, toward a detailed mechanistic understanding of fundamental physiological principles and processes. This knowledge—evidence-based and predictive in nature—will, in turn, promote new strategies for prevention, early diagnosis, treatment, and cure of diseases. Moreover, if precision medicine yields a healthier, more productive workforce; better control of chronic disease; smaller, faster and more successful clinical trials; and avoidance of unnecessary tests and ineffective therapies, the slope of the health care cost curve could decline—a welcome outcome in the United States, where health care costs are >17 percent of GNP, and still rising unsustainably. So, precision medicine holds promise for improved health and less disease, and of broad impacts—scientific, societal and economic.

Thank you, Mr. Chairman. This concludes my testimony. I shall be happy to respond to any questions.

Senator CRUZ. Thank you very much, gentlemen. I thank each of you for your learned testimony and for the time you have taken in preparing to come before this committee.

I want to start by focusing on research into medical cures. If you look at six of the diseases that impose the highest costs, both in terms of human sufferings and lives lost and in terms of dollars and cents that are spent with treatment, we have heart disease where in 2010 $444 billion was spent in treatment. In Fiscal Year 2014, we spent $1.2 billion in medical research on heart disease.

In 2010, cancer, we spent $77 billion in direct costs dealing with treatment as a result of cancer. On the research side, we put $5.4 billion in Fiscal Year 2014 into cancer research.

If you look at chronic lower respiratory disease, in 2010, roughly $50 billion in treatment costs was spent for chronic obstructive pulmonary disease. We invested approximately $1.5 billion in medical research in fiscal year 2014.

Stroke in 2010, we spent over $71 billion in medical treatment, and yet in Fiscal Year 2014, invested just $291 million in medical research.

Dementia and Alzheimer's, in 2015, it is estimated that we will spend $226 billion in treatment for Alzheimer's, a truly terrible disease my grandmother died of. Yet, in Fiscal Year 2014, we are investing just $666 million in medical research.

Finally, diabetes, in 2012, we spent $245 billion in direct treatment costs, and invested roughly $1 billion in medical research.

All total, for those six diseases, we are spending over $1.1 trillion a year in treatment costs, and we are investing collectively about $9.9 billion in medical research.

My question to the members of the panel is, does that ratio seem appropriate, not only in terms of dollars and cents, but in terms of the human lives that are dealing with the terrible consequences of these diseases?

Mr. HUBER. Could I just ask a question? Are you including all private investment or is that just government?

Senator CRUZ. That is government investments. That is not focusing on private research, that is focusing on the NIH and other government-sponsored research.

Mr. HUBER. I know quite a few drug companies who would love to cure Alzheimer's. I would go even further. Drugs are cheap at the price, they really are, even when the sticker shock is enormous. It is much cheaper to churn out cures in vats and then ship them everywhere than to have beds with people hovering over them. I think that is seriously under appreciated.

I might add there is a solution to the sticker shock problem. We get these new drugs coming out and reading stories all over about $30,000 a pill and stuff like this. Congress is responsible for this because those numbers—these are early adopter problems. We are loading all of the costs of developing a really important new drug on a very narrow window of time and therefore a small number of patients.

There are ways to spread these costs—the costs of these drugs and databases that ought to be built and are being built regardless one way or another and that are going to be saving lives for generations to come. Human bodies change over time, but basically we do not evolve as fast as fruit flies. Our children and grandchildren are going to look pretty much like us, and they are going to be cured by the same drugs. Spreading these upfront costs of treatment much more evenly, and you will take away the sticker shock.

The solution is not to say let's just tell the drug company we will not buy this stuff, we will take our ball and go home. If you do that, you are going to put the patient in the hospital and spend even more. It can be done. There are schemes for spreading costs

more evenly. I have outlined some myself. Spread the costs some more.

Senator CRUZ. Dr. Coburn?

Dr. COBURN. First, I would tell you that I think the NIH is woefully under funded. I do not think you would have any problem finding the money because as you guys know, I can show you $260 billion to $270 billion worth of duplicative things that are not generating anything for the American public today.

I think we are way underfunded, but I think we need to have better oversight because they make some errors in funding that are just plain stupid and cause people not to want to support them.

I think funding is important, but I think also this idea—it is really important that every member of this committee gets this—the way we are going to approve new drugs in the future has to change. We cannot spend $2 billion and take 10 years to approve a new drug, especially when we have precision medicine, with novel new ways of actually knowing the molecular pathways the disease is progressing through, and then using tremendous massive computer analysis of looking backward, not just looking forward, but looking backward.

Dr. Yamamoto's own organization on oat cell carcinoma and carcinoid syndrome and carcinoid cancers has already proven that you can do this.

It has to change. You cannot use what has been the gold standard for the last 50 years, which is the double blind placebo controlled, and expect to get faster products more economic, and you are not going to get capital.

If we change the way that we actually protect intellectual property, incentivize investment, you are going to get money pouring in, more money pouring in. If you enhance NIH to $60 billion a year, which is what I would do, you would also get another $30 billion or $40 billion in the private sector going into it as well, but it all hinges on how does the FDA respond to the new technology that is out there, rather than shutting it down, how does it become collaborative.

Senator CRUZ. Let me ask a final question on this, if we were to set a moon shot goal of developing breakthrough cures for each of those six diseases we discussed, in the judgment of the experts on this panel, what specific policies or tools, whether Federal research dollars, FDA reforms and changes and incentives, prizes, what tools in the judgment of this panel would have the greatest efficacy incentivizing the development of those breakthrough cures?

Dr. Yamamoto?

Mr. YAMAMOTO. I will address that question directly, but let me back up and first say that the numbers that you cited I think are problematic at both ends. That is the amount of investment we make in research and the health care costs that are being expended.

Let's start with health care costs and then I will get back to your specific question. The fact is that we are in a policy and economic era in which the expenditures for health care do not correlate in a simple way with the cost of development of drugs or devices.

Drug companies have one way to make money, and that is to sell drugs that get approved by the FDA. That means the prices are re-

flective of not only the cost of development of the drugs that get approved but also includes the cost of the drugs that did not get approved. There is no other way for the companies to make money.

Given that reality, it seems that we have in our hands the potential to be able to be much wiser about the ways we create and test drugs based on some of the things I talked about. Knowing the mechanism of a disease changes entirely the profile by which tests are carried out.

I will give you a specific example from a drug that is well known. When Sue Desmond-Hellmann was vice president for product development at Genentech, she was charged with making a decision about whether to move forward with a Phase III clinical trial for a drug candidate that eventually became Herceptin, a drug that has helped so many metastatic breast cancer patients that overexpress a gene called HER2.

It turns out that they knew at the company the drug candidate they had was attacking this HER2 protein because they had done the basic research that identified HER2 as a marker.

She asked the thought question: what would have happened at Genentech if they did not know that mechanism, and that instead they simply knew they had a drug candidate that seemed to be working on some metastatic breast cancer patients and not on others. Taking us through the numbers, she shows that the length of the trial and the size of the patient cohort would have been so long and so large that the company would have decided not to carry out the trial, and there would never have been a drug.

Other Phase III trials fail because a very small number of patients react badly or die, in the course of the trial. Two patients do not make it through Phase III and the FDA rules the drug candidate a failure, the drug company goes back to square one and starts over.

If we knew the mechanism by which those two patients had failed the drug trial, then a black label indication could protect patients with that negative indication from prescriptions for that drug, and there would be a drug effective for others on the market.

You can see this amplifies very strongly this idea that we are going to increasingly have drugs that are tailored to specific small population sectors. This concerns some drug companies because of the way our drug regulation currently works, but if we could change that profile so that drugs could be tested in a more open and transparent way, then we could, for example, reveal the results of negative trials, currently is not permitted, then we could focus on mechanistic studies that could advance trials.

We would be able to move that cost expenditure curve very substantially, and this is true with devices and other things as well. I am just using drug development as one example.

On the other side of your problematic numbers, Mr. Chairman, increased investment in research, you asked what would actually make a big difference, sustainably increasing Federal funded for research would make a huge difference, because we have in our hands, as Dr. Coburn said, the opportunity to be able to determine the mechanisms of disease, to go to the root causes, find cures and actually be able to prevent diseases that are now costing our society so much money.

That incentive for scientists to be able to carry out the work that we know can be done would not only change the outcomes of the knowledge discovery that is needed but as you said at the beginning of your comments, would incentivize the private sector to enter the arena and go forward.

Drug companies cannot do basic research. One of the main reasons that it has pulled back, as you pointed out, is that the success of a pharmaceutical company is measured in quarter over quarter and year over year performance. Basic research does not work that way. Companies are forced to make business decisions that dictate the kind of work that they can do.

What we need is increased, more effective partnerships—between academic researchers, researchers in national laboratories, and at the NIH, and pharmaceutical companies. We know how to do the things that would incentivize increased activity at the private sector end as well.

I think that the main incentive would be to increase funding for research at the basic level. This is where only the Federal Government can effectively contribute and would substantially increase the flow in the rest of the pathway.

Senator CRUZ. Very briefly because we are over time, Mr. Huber.

Mr. HUBER. I am glad that the two doctors at this table both say understanding the mechanism of action of diseases and one might add drugs, the two have to go together, is very important.

I would add the private sector has recognized this. Google and Amazon are in a race now to build the biggest data bases of DNA evidence and clinical evidence. These people are really good at analytics. They know more, I guarantee you this, about software and computers than most of this city and certainly more than the FDA does, and the statistical tools you need for this are very elaborate. They are predicting a 10 or $15 billion industry emerging. I expect they will be right.

There are precision oncology services that are operating now commercially. There is a private sector there, and some of you I believe are favoring private initiative. There is a lot of private initiative, and I am sure there are ways to incentivize that as well.

Meanwhile, the NIH does have a $230 million project going to investigate, Alzheimer's is on their list for mechanistic analysis, and they have four other diseases. They have 10 drug companies pitching in money as well. It is being done through the FNTH.

I am all for doing it in government but I will tell you, the FDA has not led the way on this, and the private sector has. The doctors are doing this and the drug companies are doing this insofar as they can. They need it to find targets for their drugs.

I would look creatively at moving outside the city, too.

Senator CRUZ. Very good. Thank you. Senator Peters?

Senator PETERS. Thank you, Mr. Chairman, and thank you for your testimony, the panelists today.

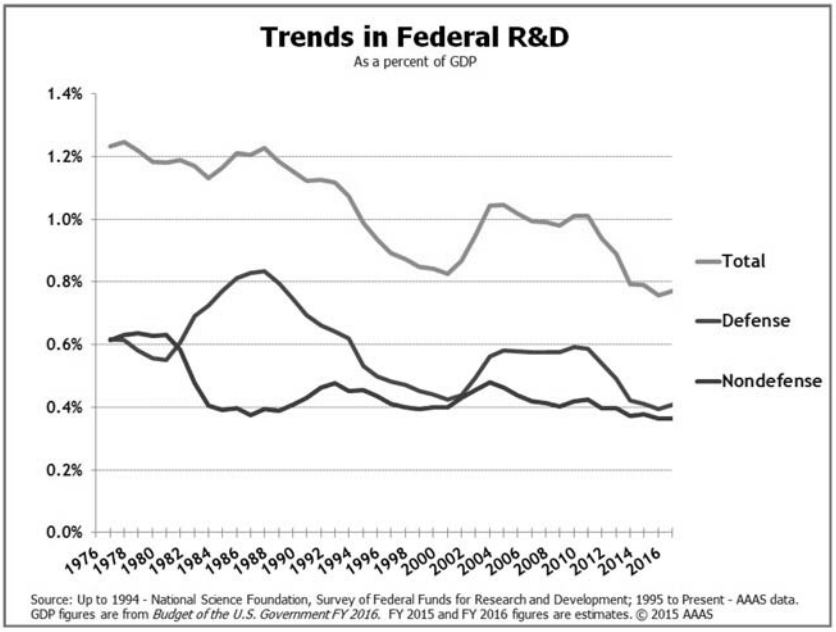
I just want to follow up a little bit. Dr. Yamamoto, you talked about the importance of investing in basic research and how important that is. As I mentioned in my opening comments, that has been declining.

In fact, Mr. Chairman, I would like to introduce another chart that actually goes beyond the one I introduced previously, just to

kind of track where trends in R&D funding have been in this country as it continues to slow downward, particularly after the sequestration and arbitrary caps we have put in place, if I could enter this into the record as well.

Senator CRUZ. Without objection.

[The information referred to follows:]



Senator PETERS. Thank you, Mr. Chairman. We are continuing on this downward slope in basic research, which is our basic seed corn for our country. I have one question related to that just to kind of follow up with you, Dr. Yamamoto. You mentioned the CRISPR technology, which is a very powerful technology.

As promising as CRISPR is, as you alluded to, the researchers were not looking for a huge medical breakthrough but rather they were collaborating with an environmental scientist on a very obscure bacterial project, research project.

What lessons should we here in Congress take away from that? Maybe Mr. Huber you would like to add to that if you would like. Dr. Yamamoto?

Mr. YAMAMOTO. Sure. CRISPR is a great example of a basic research study that was funded to characterize the genomes of weird bacteria that thrive in adverse conditions, very high metal and acid content in a SuperFund clean-up site.

It would be impossible to predict that such arcane work would eventually lead to probably the most stunning technological advance in the course of my career— and I am in my 40th year of research support for my laboratory from NIH and NSF— the greatest potential immediate application for both basic research and ap-

plication in medicine and other fields of societal interest and import.

The very unpredictability of that outcome underscores the values of basic research and the role of the Federal Government in supporting it. Vannevar Bush said it first in 1945 in his remarkable essay, "Science, the Endless Frontier." President Roosevelt had asked him to project the ways government should remain involved with scientists following the World War II effort.

He surprised perhaps everyone by asserting that the Federal Government should support basic research, with confidence that the private sector would learn from that work to develop applications.

Current day examples like CRISPR demonstrate dramatically that we must continue to be supportive of fundamental inquiry, and that we can rely upon the brilliance and creativity skills of basic scientists to see how the fundamental discoveries can be brought to application in the private sector.

Senator PETERS. I would like to go beyond that, too, if we may, broader than looking at some of the basic biological research. In your testimony, you state that precision medicine "Will depend on the engagement of wide stakeholder communities," including social scientists as well.

When we are talking about basic research, it does not necessarily mean some of the hard sciences, chemistry, physics and others. What role do you envision that social and behavioral scientists may play in making precision medicine the success that it promises to be?

Mr. YAMAMOTO. You know, it is interesting. I am a molecular biologist. I think many in my field bought into the idea that what we do is objective, firm, and solid. I was trained this way at Princeton—whereas the work of the social scientists is relevant but perhaps not "real science."

The formulation of precision medicine demonstrate that this is a very misguided notion—that not only can we discover how social forces, behavior, environment, exposures, childhood nurturing, come into play in real people's lives, but that we can correlate information about those elements to the objective data that I was comfortable with, resulting in a much clearer understanding propensity for disease and the course of disease.

What we have learned in precision medicine is that all of these parameters need to be considered. Now more than ever with this opportunity in precision medicine we need to be collecting data on social and behavioral elements and their impact on disease, so those scientists and their work should be increasingly important.

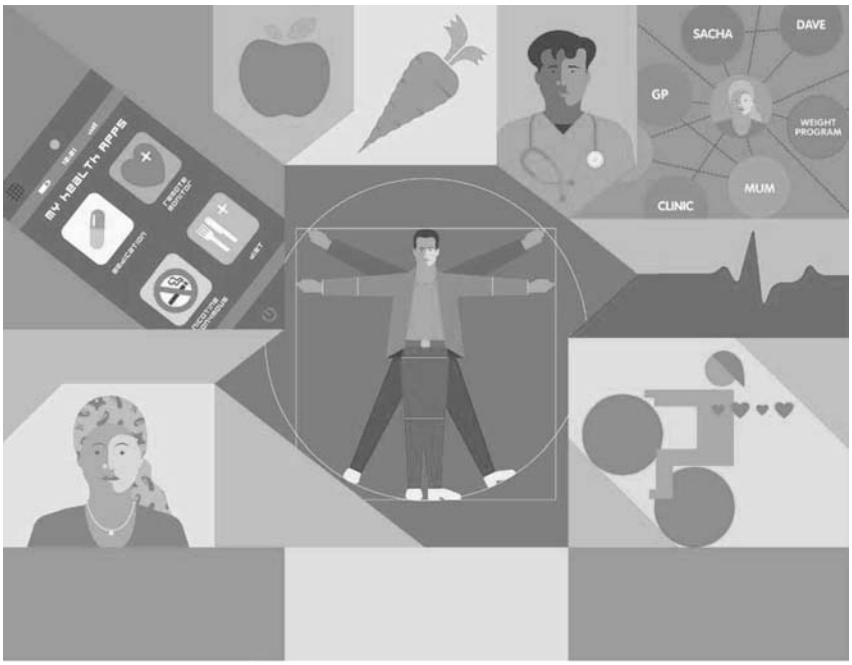
Senator PETERS. Along those lines, if I may, Mr. Chairman, I am entering a number of things in the record here, if I could add another one. It is a report from McKinsey that talks about "Changing Patient Behavior, the Next Frontier in Health Care Value," which I think goes along the lines of what Dr. Yamamoto is entering, if we can enter this into the record as well, I would appreciate it.

Senator CRUZ. Without objection.

[The report referred to follows:]

CHANGING PATIENT BEHAVIOR: THE NEXT FRONTIER IN HEALTHCARE VALUE

By Sundiatu Dixon-Fyle, PhD; Shonu Gandhi; Thomas Pellathy; and Angela Spatharou, PhD



Changing patient behavior: the next frontier in healthcare value

To address the rising cost of chronic conditions, health systems must find effective ways to get people to adopt healthier behaviors. A new person-centric approach to behavior change is likely to improve the odds of success.

Sundiatu Dixon-Fyle, PhD; Shonu Gandhi; Thomas Pellathy; and Angela Spatharou, PhD

Changing individual behavior is increasingly at the heart of healthcare. The old model of healthcare—a reactive system that treats acute illnesses after the fact—is evolving to one more centered on patients, prevention, and the ongoing management of chronic conditions.

This evolution is essential. Across the globe, a fundamental shift in healthcare risk is taking place, driven by an aging population and the increasing incidence of behaviorally induced chronic conditions. Health systems are innovating on the delivery side to meet this challenge through a growing emphasis on primary care, integrated care models, and pay-for-value reimbursement.

Yet more must be done to reorient health systems toward prevention and the long-term management of chronic conditions. In an analysis we conducted of US healthcare costs (which are now nearing $3 trillion annually), 31 percent of those costs could be directly attributed to behaviorally influenced chronic conditions. Fully 69 percent of total costs were heavily influenced by consumer behaviors. Poor medication adherence alone costs the United States more than $100 billion annually in avoidable healthcare spending.[1] The burden consumer choices place on low- and middle-income countries is similarly staggering: Harvard and the World Economic Forum have estimated that noncommunicable diseases result in economic losses for developing economies equivalent to 4 percent or 5 percent of their GDP per annum.[2] Unless health systems find ways to get people to change their behavior (in terms of both making healthier lifestyle choices and seeking and receiving appropriate preventive and primary care to manage their health conditions), they will fail in their quest to tame healthcare costs without impairing care quality or access.

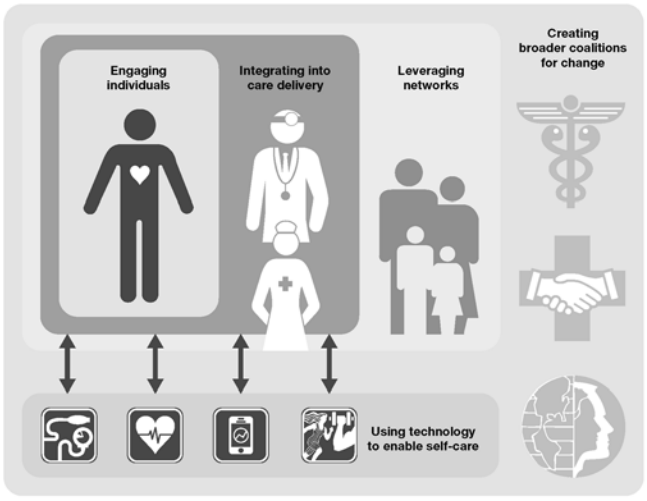
Designing and implementing programs that enable people to achieve sustainable behavior change is hard. Few programs tried in the past achieved sustained impact. However, many of these interventions were rooted in the old model of healthcare, focusing on the treatment of clinical problems after an acute event. Too often, the interventions had poor program design, insufficient measurement rigor, and implementation issues. The failures led many health system leaders to be skeptical about whether *any* behavior change program can achieve long-term impact.

We believe that behavior change programs can succeed, but only if their design paradigm is rethought. This article describes an emerging approach—a *person*-focused paradigm that uses a behaviorally based rather than disease-based orientation to drive sustainable behavior change. Instead of assuming that individuals are fully rational, it recognizes that human decision making is affected by systematic cognitive biases, habits, and social norms. Instead of focusing exclusively on the clinician-patient relationship, it seeks to create a supportive ecosystem that engages individuals and those closest to them.

Our perspectives draw on an analysis of global trends, our extensive experience working with clients throughout the healthcare industry on this topic, and interviews with leading experts. They are grounded in emerging insights from the behavioral sciences that shed light on how individuals actually make decisions, as well as new technological advances. Leveraging these insights, we have developed an integrated framework to help healthcare organizations across the value chain understand the new paradigm and how they can design and implement high-impact, patient-focused interventions.

[1] Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487-97.
[2] Bloom DE et al. *The Global Economic Burden of Noncommunicable Diseases*. World Economic Forum and Harvard School of Public Health. 2011.

Exhibit 1 **New paradigm for patient behavior**



Elements of the paradigm

The new person-focused paradigm for behavior change has five major components (Exhibit 1):

- Engaging individuals more effectively by taking advantage of new insights from behavioral psychology and behavioral economics
- Integrating behavior change as a core component of new care delivery models
- Using the power of influencers and networks to support behavior change
- Utilizing remote and self-care-oriented technologies to support and empower individuals, and connect them to clinicians and other influencers
- Adopting a multi-stakeholder approach, which includes public-private partnerships, to support high-impact societal and primordial prevention interventions

Engaging individuals

Insights from behavioral sciences are being widely used in financial services, retail, and other sectors to influence what we buy, how we save, and other aspects of our behavior. Yet the

design of most health-related products, services, and interventions remains remarkably unaffected by these discoveries into how humans make decisions. For example, traditional clinically driven interventions assume that individuals understand their own health issues and usually act rationally to address them; however, this is often far from the case. In a survey we recently conducted, 76 percent of the participants with high-risk clinical conditions described themselves as being in excellent, very good, or good health (Exhibit 2). Programs that fail to account for this gap between individuals' actual health status and how they understand and experience their health on a day-to-day basis (and thus how willing they are to change their behavior) miss the boat in terms of design. Often, these programs simply attract individuals who are already "activated" to change their behavior, rather than reaching those who need help before they can take proactive steps to improve their health.

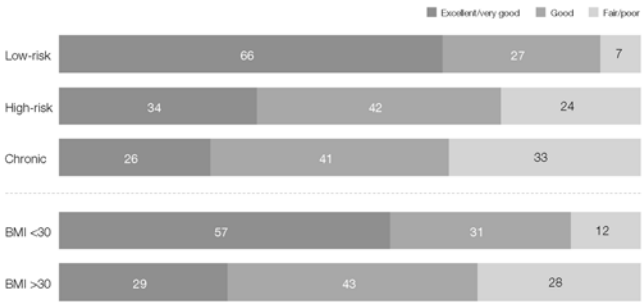
What does good design look like? With regard to behavior-change interventions, three innovations appear to be most important.

Behaviorally based segmentation should be used to deepen insights into specific groups. Current approaches to patient segmentation and predictive modeling tend to center on clinical conditions. However, change interventions are more likely to be successful if they take into account additional factors, such as a person's behavioral profile or motivation to change. These insights enable more focused targeting of the groups of people for whom impact is most likely to be achieved. They also make it possible to design programs that more effectively address practical barriers to change.

Exhibit 2

Most people think they are significantly healthier than they are

Respondents' self-assessment of their health status by different risk categories,[1] %



[1]Based on derived health profile.

Source: McKinsey Retail Healthcare Consumer Survey

"Incentives that take people's cognitive biases (e.g., loss aversion, regret aversion, optimism, and present-biased preferences) into account are more effective than direct cash rewards."

For example, most programs geared to "ER frequent fliers" or people with high hospital admission rates target patients through risk-, disease-, or condition-based retrospective reviews of high-cost episodes. Incorporating additional behavioral insights permits a more nuanced approach. In a recent project for a large US payor, we used demographic, family structure, and consumer purchase data (e.g., nature of purchases, car ownership, etc.) to construct a social isolation index (a variable intended to measure each individual's degree of social connection) for the target population. When combined with claims data, this index enabled us to more effectively predict, among groups with equivalent at-risk chronic conditions, which people were likely to have a high-cost emergency room admission or inpatient event.

We found, for example, that hospital costs were 24 percent higher for socially isolated individuals than for socially connected individuals with an equivalent level of clinical risk, and that the socially isolated individuals also had lower prescription drug use. Such insights can help identify key patient subgroups before high-cost episodes occur by "typing" members against defined predictors; interventions targeted toward these subgroups can then be designed with the right focus (e.g., field-based extender services and medication adherence interventions for socially isolated individuals).

"Person-focused pathways" should be used to support people as they attempt to alter their behavior. Most disease management programs remain rooted in a clinically based view of the world. For example, they may correctly identify a patient with diabetes or another chronic condition, but do not fully address the fact that the same patient may also be overweight, suffer from heart disease, have mild-to-moderate depression, mistrust his clinician, and be socially isolated.

Clinical insights are critical, but our experience shows that program designs are more effective when they directly address the root causes and barriers to behavior change and provide interactions with the right timing and frequency to ensure impact. In essence, these designs translate clinical insights into person-focused pathways that support individuals from the point at which they decide to make changes to the point that the new behaviors are sustained.

A simple example demonstrates the impact of guiding patients to the behavior-change interventions that are most suited to them, based on their needs. In England, we worked with a regional payor to improve diabetes care by defining behavioral segments among affected patients and then matching the right portfolio of support programs to each segment. General practitioners were trained to identify which segment patients belonged to by asking a few

simple questions and then to direct them to the behavior change intervention that best met their needs. This simple steerage led to a nine-fold increase in program enrollment (from 7 percent to 63 percent) within six months and, more importantly, to a higher rate of program completion. Similarly, even very simple defaults, such as automatic mail-order enrollment for prescription renewals, can help address patients' barriers to adherence.

Active communication along the pathway is also critical, because frequent feedback encourages behavior change. A study on weight loss we conducted with leading behavioral economists suggests that giving people frequent, automated feedback helps improve weight loss.[3] Text messaging is being increasingly used to support patients with diabetes or other chronic conditions and to send them educational materials, medication reminders, and tips on disease management; preliminary results are encouraging.

Behaviorally based incentives should be used to encourage change. Incentives are an increasing part of the toolkit for addressing behavior change. Two-thirds of US companies, for example, now offer employees financial incentives to encourage healthy behaviors.[4]

Well-designed incentive programs have demonstrated impact. Discovery's Vitality program, for example, informs members about their health status, encourages them to set behavior-dependent health goals, and then rewards them for attaining those goals. Members earn points for behaviors ranging from undergoing diabetes screening to healthy purchases in supermarkets, and in turn receive a mixture of short- and longer-term rewards, including cinema tickets and discounted flights. Discovery estimates that the program has lowered participants' overall healthcare costs (on a risk-adjusted basis) by about 15 percent.[5] Innovative corporate wellness programs, such as those offered by Limeade, are also gaining traction.

The structure of the rewards matters. Incentives that take people's cognitive biases (e.g., loss aversion, regret aversion, optimism, and present-biased preferences) into account are more effective than direct cash rewards. We recently tested behaviorally based incentives using a "regret lottery" design.[6] The goal was to get a company's employees to complete a health risk assessment. Half the employees were given cash incentives directly; the others were divided into small teams that were then enrolled in a lottery. Each week, one team would win the lottery, but rewards were distributed only to team members who had completed the assessment. The winning teams were widely publicized to leverage anticipated regret (people's disinclination to miss their chance of winning the big prize the week their team was selected). The result: 69 percent of the employees in the lottery completed their assessments, compared with 43 percent of those given direct incentives.

[3] In press.
[4] *Performance in an Era of Uncertainty*. 2012 Tower Watson employer survey results.
[5] Morris G. Presentation about Discovery's Vitality program. Oxford Health Alliance Summit. 2010
[6] Haisley E et al. The impact of alternative incentive schemes on completion of health risk assessments. *Am J Health Promot*. 2012;26:184-188.

Integrating behavior change into new care delivery models

Many health systems are putting increased emphasis on primary care, especially through the use of integrated care delivery models designed to improve the health of the population. To succeed, these new models must extend their reach outside of the four walls of a clinician's office so that they can support patient behavior change beyond traditional clinician-patient interactions. This requires new capabilities, including clinical workflow tools to support patient targeting, care alerts sent to both clinicians and patients, enhanced communication and care management support for patients, and remote monitoring. More fundamentally, clinicians must adopt a patient-centered approach when they interact with patients, one that focuses on understanding the whole person and their barriers to change.

A good example of this kind of model is CareMore, a California provider that focuses on seniors. One of its primary goals is to encourage behavior changes crucial for effectively managing chronic conditions. CareMore combines technological innovations, including electronic medical records (EMRs) and remote monitoring, with a wide array of nontraditional services (e.g., caregiver support, preventive podiatry, no-cost transportation to its offices, house calls by physicians and nurse practitioners, tailored fitness centers, and an intervention team that goes to patients' homes to investigate nonclinical problems).

CareMore reports that its risk-adjusted costs are 15 percent lower than the regional average for comparable patients and its clinical outcomes are above average. For example, its amputation rate among diabetes patients with wounds is 78 percent below the national average, and its rate of hospitalization for end-stage renal disease is 42 percent below that average.[7]

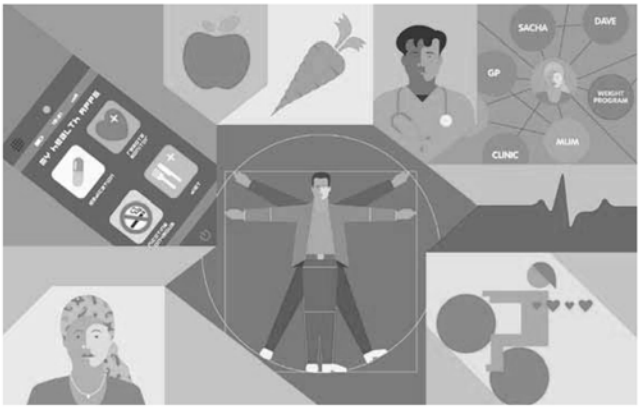
Using the power of influencers and networks

Health choices are not made in a vacuum. Our research shows that when faced with a health event, people follow the treatment advice of friends and family 86 percent of the time. Some health promotion efforts already recognized the importance of these influencers. For example, adult smoking cessation programs in the United Kingdom and elsewhere are increasingly targeting young children, because parents who smoke are more likely to respond to their children's concerns than to the prospect of their own poor health.

Payors and providers have also come to appreciate the power of influencers to support behavior change and have used peer programs with considerable success. In Philadelphia, for example, the US Veterans Affairs (VA) Medical Center created a peer program to encourage better diabetes self-management among African-Americans (a group with a higher-than-average prevalence of diabetes and a significantly increased risk for complications). The program first identified "mentors"—other diabetes patients who were already keeping their glucose levels under good control—and gave them training. Program participants were then assigned

[7] Reuben DB. Physicians in supporting roles in chronic disease care: the CareMore model. *J Am Geriatr Soc.* 2011;59:158-60.

"Health choices are not made in a vacuum. When faced with a health event, people follow the treatment advice of friends and family 86 percent of the time."



mentors with the same demographic background (gender, age, etc.). The participants and mentors interacted on a weekly basis, primarily by telephone. After six months, the participants had achieved an 11 percent drop in their average glucose levels (from 9.8 percent to 8.7 percent), a change sufficient to decrease their risk of disease-related complications.[8] In contrast, a control group of patients who did not have mentors experienced no improvement in their glucose levels during the study. Nearly two-thirds of the participants in the peer program said that having a mentor who also had diabetes was important in helping them control their own glucose levels.

As the VA program demonstrates, peer-based networks can be relatively easy to implement. As long as the peer matching is done in a way that resonates with participants, these networks can provide an additional support system to help sustain behavior change.

[8] Long JA et al. Peer mentoring and financial incentives to improve glucose control in African American veterans: a randomized trial. *Ann Intern Med.* 2012;156:416-424.

Utilizing remote and self-care-oriented technologies

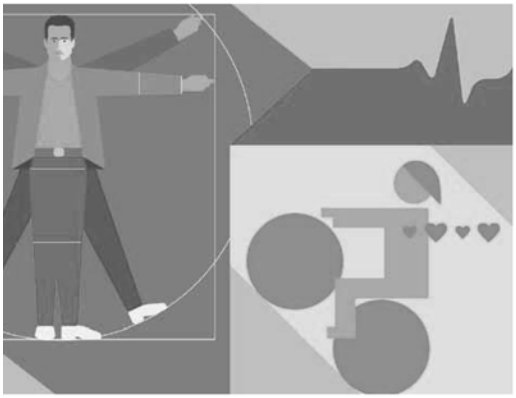
Frequent, real-time communication and feedback are important in supporting change efforts. Traditional models of care delivery have, at their core, face-to-face interactions between clinicians and patients. New technologies, however, are augmenting this interaction model and fundamentally transforming the ways in which clinicians deliver—and individuals and their friends and family consume—care. Mobile apps, for example, can facilitate tracking and monitoring. Wireless devices can transmit adherence information directly from pill boxes, scales, or even ingested "smart pills." Webcams enable remote consultations. Ultimately, these remote and self-care-oriented technologies may help create a truly interactive healthcare ecosystem for patients.

Many of these new technologies are gaining traction, particularly in developing countries,

where access remains an issue. However, they are also being increasingly used in more developed countries. In the United Kingdom, for example, a large trial of telehealth devices for patients with social care needs and chronic conditions has produced positive results. Participants received either home monitoring equipment or a set-top box that could be connected to their TVs; the devices enabled patients to ask questions about their symptoms, gave them visual or audio reminders when measurements were due, showed educational videos, and charted a graphical history of recent clinical readings. In the trial, telehealth device use appeared to reduce the number of emergency room visits and hospital admissions, as well as one-year mortality rates.[9] Studies among US Medicare and VA patients have also shown that telehealth devices decrease healthcare utilization. In these studies, use of the devices has produced savings of up to 13 percent.[10]

[9] Steventon A et al. Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomized trial. *BMJ*. 2012;344:e3874.

[10] Baker LC et al. Integrated telehealth and care management program for Medicare beneficiaries with chronic disease linked to savings. *Health Affairs*. 2011;30:1689–1697.



Adopting a multi-stakeholder approach

There is increasing recognition that if health systems are to address the full range of issues adversely affecting patients' health, healthcare leaders will need to partner with a broader set of stakeholders to create an environment conducive to driving healthier behaviors and achieving impact. We have worked closely with clients attempting to create such broad coalitions, which we believe are crucial for achieving strong, sustained behavior changes.

For example, we worked with major retailers and food manufacturers in one country to address the challenge of obesity by creating a "movement" to raise awareness and spur consumers, employers, children, communities, and organizations to action. With the support of a multi-stakeholder coalition, a plan was developed in which the CEOs of participating retailers and food manufacturers committed their organizations to certain targets and actions. These ranged from healthy school partnership programs, workplace fitness and nutrition programs, and joint manufacturer/retailer initiatives to lower caloric intake and increase caloric transparency. Although the economic impact and health consequences of these types of efforts are hard to quantify, they are critical in creating an environment that supports more direct interventions.

More direct impact can be achieved through appropriately focused government interventions and public-private partnerships. A classic example is increased taxation on cigarettes, but more creative interventions are also possible. In Argentina, for example, a government-sponsored conditional-transfer program aims to reduce average sodium intake; bakers have been asked to decrease the amount of salt in their bread but are directly compensated for lost revenues from lower sales.

"Re-orienting health systems around a model focused on prevention, long-term management, and patient-centered care will require top-down leadership and advocacy."

Impact and implementation

We believe that the new person-focused paradigm described here is likely to deliver stronger results than traditional behavior change programs have produced. Disease management programs rooted in the old model of healthcare typically achieve savings in the range of 2 percent to 5 percent of medical costs. Based on our experience and the studies published to date, we estimate that programs designed under the new paradigm could deliver a 10 percent to 15 percent reduction in those costs in target populations, in addition to productivity gains, better outcomes, and better quality of life.

Implementation of the new paradigm is challenging, though. One significant issue is scalability: while many of the needed elements exist and pilots abound, there are few instances of anyone applying all of the design elements at scale. The cost of building the underlying infrastructure (e.g., platforms to administer incentives and provider EMR systems to enable effective patient insights) is also an issue—although, in most cases, low-tech, cost-effective approaches exist, and ongoing innovation is simplifying and lowering the price of many technologies.

The biggest obstacle, however, is the mindsets of healthcare leaders and clinicians. Most remain rooted in the old model of healthcare. Many are highly skeptical of behavior change programs; some do not even consider behavior change as part of a health system's remit. These attitudes hinder the fact-based evaluation of behavior change programs and the adoption of proven successes.

Re-orienting health systems around a model focused on prevention, long-term management, and patient-centered care will require top-down leadership and advocacy. Such leadership is necessary if health systems are to meet the coming wave of healthcare challenges.

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If health systems are to address the shifts in healthcare risk now taking place—especially those resulting from chronic conditions—they must find ways to get individuals to adopt healthier behaviors. New behavior change programs based on a person-focused, rather than disease-focused, paradigm are proving that it is possible to achieve strong, sustained results. However, a change in mindset is required if these programs are to gain widespread use. ○

Sundiatu Dixon-Fyle, PhD, a practice expert in McKinsey's London office, supports payors and providers on strategies for patient-centered care. **Shonu Gandhi,** an engagement manager in the Washington, DC office, works extensively on consumer engagement with payors. **Thomas Pellathy,** a partner in the Pittsburgh office, concentrates on helping health systems improve healthcare value. **Angela Spatharou, PhD,** a partner in the London office, focuses on strategic issues, including integrated care, for healthcare providers.

Senator PETERS. Thank you. This report suggests that more than two-thirds of the health care costs are heavily influenced by consumer behaviors, and yet interestingly enough, the National Science Foundation Social Behavior and Economic Research Account is under constant attack here in Congress for the efforts they make and some of the funding that goes into those efforts.

Just a final question, as we are out of time here, Dr. Yamamoto, there is roughly $250 million to $300 million per year that the NSF currently invests in social and behavioral science, which is a very tiny fraction of the total amount that is spent, and yet it is a significant portion of what we need to know and understand in order to have effective treatments and effective research.

Do you think it is wise to redirect? Some in Congress have asked to redirect that $250 million to $300 million to some other areas of science. Are we in fact under investing in what is a critical area?

Mr. YAMAMOTO. We are definitely under investing. As I said, it is increasingly important. I can actually cite a clinical trial, a very interesting one, that was done for diabetes, one of the major disease areas that Senator Cruz mentioned in his opening comments.

There were four arms to the trial: Metformin, which is the standard drug that is given for Type 2 diabetes, a new drug candidate, a control, and finally a set of imposed behavioral changes. It turns out that trial arm for the new drug candidate was stopped early because of adverse effects, and that the recommended behavioral changes/modifications actually outperformed the standard drug, Metformin.

We need to be able to continue to pursue these studies. And because it is not just in medicine that these social/behavioral elements are important, it is fully appropriate that such work be supported by the National Science Foundation.

Senator PETERS. Thank you.

Senator CRUZ. Thank you. Senator Wicker?

STATEMENT OF HON. ROGER F. WICKER,
U.S. SENATOR FROM MISSISSIPPI

Senator WICKER. Thank you, Mr. Chairman. I think this is a pretty exciting hearing. It might seem small and not well attended. In terms of the future and in terms of alleviating human suffering and saving a ton of money for the taxpayers, this may be the most important hearing we will have all year.

I appreciate the brain power in front of me, and I appreciate having an opportunity to have a little give and take.

Senator Coburn, my friend of 21 years now, is back here and he is looking good, he is once again making a lot of sense. Senator Coburn mentioned risks, transparency, and peer engagement at FDA. I hope the House legislation is improved on, I hope it passes, I hope the FDA is listening. I would commend to everyone's attention a simple straightforward bill that I have introduced called the Patient Focused Impact Assessment Act.

This bill was introduced with the help of my friends in the Duchenne community. It would promote transparency by simply requiring the FDA to share how they use patient and advocate input in the approval process. I would commend that bill to the attention of the members and suggest it would be a small step.

Let me say how thrilled I am that Chris Frangione is here, and I appreciate the work that he has done with me and my staff in moving toward introducing legislation later on this year to create a prize working with the XPRIZE foundation, trying to work in partnership with NIH on developing a prize and identifying achievements with regard to curing and alleviating suffering from Alzheimer's.

Chris, you mentioned that you do not care who wins the prize. It could be somebody that is in college. It could be somebody you hardly expect.

A lot of us are reading David McCullough's book on the Wright Brothers. Who would have picked out two bicycle manufacturers from Dayton, Ohio to give a grant to create the machinery that would crack this problem of human flight. As a matter of fact, government agencies on both sides of the Atlantic were awarding grants to other people. It happened these people were working toward the formula and used a scientific method, tried over and over again over the course of years, and actually got it done. I appreciate what you said about that, Chris.

Let me just say that with regard to Alzheimer's, I do think this may be a critical moment. Mr. Chairman, you mentioned 700,000 people will die this year from Alzheimer's Disease. A breathtaking number. It is also the most expensive disease in America. Of course, we know it is 100 percent fatal.

A report released earlier this year estimates that the caring for people with Alzheimer's will cost the United States $226 billion this year, including $153 billion to Medicare and Medicaid. In 2015, one in five Medicare dollars will be spent on someone with Alzheimer's, one-fifth.

Unless we find a cure or a new drug therapy to halt the progression of this disease, treatment costs will continue to rise. By 2015, the annual costs will grow to $1.1 trillion, including a 500 percent increase in Medicaid and Medicare spending on Alzheimer's, a disease which I think we can get to.

Thank you, Mr. Frangione, and thank you to your CEO, Dr. Diamandis, for working with my staff and me and with a group called USAgainstAlzheimer's, on finding a way to encourage the Government to spur innovation in Alzheimer's research through prize-based challenges.

Later on this year, I will be introducing the EUREKA Act, Ensuring Useful Research Expenditures is Key for Alzheimer's, EUREKA. I will be asking you, Mr. Chairman, and Mr. Ranking Member, and all of my colleagues both in the Senate and the House, to work with us on this.

I appreciate the positive imprimatur of the XPRIZE Foundation in making us believe this can work. In the five minutes that I have, I will just ask one question. With the prize, you pay only for success. How much would we pay, how much would society pay for a cure to Alzheimer's, but given these numbers, in 35 short years, we will be spending $1 trillion a year, how much would society pay for a cure?

I have learned in dealing with the Foundation that there are prize-able steps that get us concrete results and save us concrete amounts of money.

If, Mr. Frangione, you could comment on that for the benefit of the Committee. Of course, the ultimate cure would be a wonderful event, we would set off fireworks around the world on Independence Day. We could do that.

How can we have prizeable events that get us concretely and amount to success that is worth paying for?

Mr. FRANGIONE. Sure. Thank you so much for your leadership, and Sarah Lloyd on your team has been great to work with. We appreciate that.

Prizes can get you along that spectrum without getting you all the way there. Getting all the way there is going to be a really, really big moon shot. There are lots of places prizes can play and one, especially as Dr. Yamamoto was talking about, is collaboration.

We see in prizes you can bring together disparate folks to work together on a problem, whether it be people from the engineering community or people from the health community or people from the social sciences or wherever.

In fact, I talked about well-designed prizes. One of the things that we do at XPRIZE is when teams register, we actually ask them are you missing any components to your team, are you looking for any other people? We also allow individuals to register that have specific expertise and knowledge that can then join these teams to build that collaboration.

In terms of Alzheimer's, you can see a bunch of different steps along the way. Imagine starting off with finding a prize that can look for the biomarkers or whatever it is that can allow us to diagnose Alzheimer's way earlier than we currently do. Right now, you are pretty far along for us to be able to diagnose you. Or as an intermediate step, we are actually working on an AI prize. Could that AI prize become an AI human brain augmentation? You can actually help people with Alzheimer's artificially bring back some of their brain functions. Or imagine you have a prize out there in robotics, so you are bringing all these people from robotics, you are creating a human helper to take away some of the burden on family members and the medical community, and you can augment a human with Alzheimer's with a robotic helper.

There are lots of different directions you could go ultimately on the way to finding that cure. You can incentivize different steps along the way.

Prizes can find cures or biomarkers, prizes can help you solve the problem, essentially put a Band-Aid on it, but a really important Band-Aid that will give somebody a much better quality of life, or prizes can help you do things through AI or Big Data. There are lots of things we could do, and we are actually looking at all those right now at XPRIZE, as are people outside of XPRIZE, looking at different ways to augment it.

Senator WICKER. Thank you very much. Thank you, Mr. Chairman, for your indulgence. Mr. Frangione, if someone within the sound of our voices today called you up and had an idea they would like to share, you would be happy to hear that, I take it?

Mr. FRANGIONE. I would be very happy to hear it.

Senator WICKER. Thank you very much, so would I.

Senator CRUZ. Thank you very much. Senator Udall?

STATEMENT OF HON. TOM UDALL,
U.S. SENATOR FROM NEW MEXICO

Senator UDALL. Thank you, Chairman Cruz, and Ranking Member Peters. Excellent hearing. I could not agree more with what others have said. It has been very insightful, and I think if we just worked with each other and took a little guidance from you, we could really make a difference on some of these issues.

Dr. Coburn, you really do bring an unique perspective from how you talked about it, and I could not agree with you more in terms of NIH being woefully underfunded, and also we need the oversight to make sure there is the credibility there.

I think the other thing the panel brings forward is you all talk about how important basic research is, and we need to be investing in the National Science Foundation's work to fund basic research at universities and that kind of activity across the country.

My first question for Dr. Frangione, I would like to ask you about XPRIZE. XPRIZE is trying to solve some of the really tough questions. You mentioned several of them, Alzheimer's, which Senator Wicker talked about, kidney disease.

As difficult as these challenges are, I think American ingenuity can solve many problems like these. We just need to get more innovators and researchers to focus. That is why I find it to be so valuable about the XPRIZE model of using challenge prizes to encourage innovation and new thinking, and as you have said, to get the interdisciplinary work going on between various parties.

In fact, I plan to introduce legislation in the Senate soon that is a companion to the House-passed Science Prize Competition Act. This legislation would update the authority of Federal agencies to encourage the use of challenge prizes to solve problems.

Agencies like DARPA, the Department of Energy, NASA already have a solid track record when it comes to challenge prizes, but I think we could be doing more to encourage other agencies to consider this approach to problem solving.

Could you expand on your testimony as to why XPRIZE supports the Science Prize Competition Act?

Mr. FRANGIONE. Sure. Thank you for your leadership on this. What we like about the Act is it just gives clearer guidance. All the agencies have authority to do prizes right now, but this gives clearer guidance on it. Everybody is doing it slightly different. You named some that are doing it really well. A lot of general counsels are interpreting the legislation differently. This Act really gives clearer guidance, and we think that is really important.

It would actually send a really strong signal to the Federal Government that the Congress supports prizes. In addition, one of the things that you are allowed to do in the government is partner with private organizations in launching prizes.

Passing this legislation would also send a strong signal to the private sector, to folks like us, non-profits or for profit prize companies, that everybody is in support of this and we should really look toward really great ways to use it.

I will give you an example of this collaboration which will help people understand how important prizes could be in playing a role in innovation. We recently concluded an ocean health prize. This is to find better sensors to measure our oceans. We do not know what

is going on with our oceans in terms of acidification right now. We are going to be awarding this on July 20.

There were a bunch of teams, and there is a high school team, a high school team that made it to the semifinals, and they could not afford to get to the semifinals. They went out and put out a GoFundMe campaign. Their largest contribution of $1,000 was from another team in the competition competing against them for $2 million. They actually funded them so they could go compete against them.

That is the type of collaboration and that is why things like this Act are really important to spur that collaboration, spur the collaboration Dr. Yamamoto was talking about, to really drive us forward as one versus a bunch of siloed expertise where people are not talking to each other, because they do not know how to talk to each other. There is an invitation to talk to each other, and a prize and prizes create that invitation for people to talk to each other if the prize is designed well.

Senator UDALL. Thank you very much. Dr. Yamamoto, I would like to ask you about precision medicine and tackling rare diseases. We have an uncommon genetic blood disease in New Mexico called cavernous cerebral malformations that impacts people of Spanish descent.

I have a piece of legislation dealing with research on that. Can you discuss some of the recent developments in precision medicine that can help tackle rare genetic diseases such as CCM?

Mr. YAMAMOTO. I think Dr. Huber pointed out that all diseases have a genetic basis—that they are grounded in some place in genetics. That is likely true. But a mutation, a "disease gene" is rarely a certain predictor of disease. We need to link those genetic alterations with other molecular parameters, as well as social, behavioral and experiential parameters.

Being able to massively collect data on genome sequences and many other factors, and then correlate those findings with defects similar to those you are talking about is going to uncover the causes of rare diseases and will allow us to attack them directly.

This is being approached in many ways. We are sequencing cancer patients at UCSF and tying those data to each patient's electronic health record, by sequencing blood spots from newborn babies, and looking for correlations with subsequent health matters through their lives.

The precision medicine approaches offer a tremendous opportunity to be able to find the root causes of rare diseases and approach them directly.

Drug companies, as you know, have been loath to try to develop pharmaceuticals, therapeutics, for rare diseases, because of market concerns. If we knew about mechanisms, again, directed work could be carried out and that would be very effective, and the drug companies would be incentivized to move forward.

Senator UDALL. Thank you very much. Thank you, Mr. Chairman.

Dr. COBURN. Can I comment on that? One of the things Dr. Yamamoto did not mention is if you do it the way he suggested, it is going to cost a whole lot less and take a whole lot less time.

$100,000 to get a cure for one of these rare diseases versus billions. It is a real shaking change in terms of outcomes.

Senator CRUZ. Thank you. Senator Johnson?

STATEMENT OF HON. RON JOHNSON,
U.S. SENATOR FROM WISCONSIN

Senator JOHNSON. Thank you, Mr. Chairman. Tom, great to see you. I thank all the witnesses here.

That is only going to work if people have the freedom to access that, and we reformed the broken model of the gatekeeper, the FDA, a completely risk adverse process.

My daughter was born with transverse resistant arteries. Two things I learned very quickly, not being a doctor, there is a reason they call it "medical practice," with emphasis on "practice." That is not denigrating the field, that is what medicine is all about, advancing it through a series of trial and error.

The other thing I learned very quickly, there are centers of excellence. I had the freedom back in 1983 to access those centers of excellence and then find the most advanced surgical technique, which is still experimental, for my daughter's condition. My daughter is 32 years old, she is doing tremendously well. Now we do the actual aorta switch. It is advanced.

Coming from a manufacturing background, I am looking for the root cause. I understand why the FDA is so unbelievably risk adverse, but when you are so risk adverse and when you do not give patients the freedom to choose, I think we are going to really hamper medical advancement in moving toward these cures.

Listen, I think it is great, XPRIZE, that is great, but a $10 million prize is not going to incentivize breakthroughs in something that literally costs hundreds of millions of dollars to develop. The prize really is a free market system. We need to let that free market system operate without the impediments of spending $100 million, cut it off because it is not worth the risk.

Dr. Coburn, you said we have to move the power back to patients and doctors. That is not the direction we are going in this country, is it?

Dr. COBURN. No, but if you see what is really happening out there right now, especially in the field of cancer, which will be applied in so many other areas—actually, I am getting a treatment product based on that very idea right now—using an approved drug for something else because we have found through precision medicine and biomarkers that it actually has application over here, FDA cannot stop that.

Senator JOHNSON. Today, they cannot.

Dr. COBURN. They are not going to stop it because of the uproar. I would make two points. FDA changed when the AIDS' activists came and said change. They demanded change. You are seeing science move so far ahead of the FDA. FDA knows they cannot keep up with this. They know they do not have the capabilities. Janet Woodcock has actually said that.

The question then comes what do you all do in legislation that takes the monkey off FDA's back. It is still responsible, but makes them the collaborative, cooperative agency that they need to be, you can still punish bad actors, but we are going to find out a

whole lot more data by being freer with the process rather than tighter.

Senator JOHNSON. The point I was trying to make with the centers of excellence, let them be more involved in the process, let the FDA cooperate with those centers of excellence for different diseases and let the process move forward.

Dr. COBURN. That is right. The great example right now is on biomarkers. They have not—they have the ability under the law to go out, set up, and have this cooperative process and bring everybody together and be transparent with it, so we actually find more and more information and share more information, but that is not happening right now.

Part of the hope with the 21st Century Cures is to actually give the FDA some relief. They need more money, I will tell you that, they do. We keep adding things to them to do, and yet their budget does not necessarily increase, so they do need more money to accomplish some of this, but also if we transition to this collaborative process where we take areas like the University of California in San Francisco and let them be one of these collaborative/cooperative areas, then what happens is in the long run, they will have less budgetary needs because they are actually in cooperation.

They cannot go out and compete with the private sector on the best and the brightest. They cannot compete with the universities and they cannot compete with the private sector. They are not going to be able to do it.

The way to move forward is in a way where we actually assume that people are going to do the right thing, not the wrong thing, and we have an agency that has everybody assuming they are going to do the wrong thing, and that is a very expensive regulatory process.

Senator JOHNSON. I also want to ask your assessment of two other large dangers, I think, as it relates to advancement in innovation, and that is the medical device tax, which I think is a tax that literally is shipping jobs overseas, certainly restraining investment in medical device manufacturers, but also the Independent Payment Advisory Board, those two aspects of Obamacare.

Can you comment and give us your assessment of how those two measures are hampering innovation?

Dr. COBURN. We have already seen 40,000 to 50,000 jobs leave this country on medical devices. We will see more because the burden and the taxation both are negatives for innovation and capital formation.

We do not know what the Independent Payment Advisory Board is going to do, but the fact is—here is the other thing that I think is important in terms of new drugs, and Mr. Huber made this point. Some of the good drugs are going to be fantastically expensive, but if you measure in terms of the cost/benefit to society, they are cheap.

If they take an Alzheimer's patient and slow down the process where they have five more years of active life in terms of inputting in society that is not costing such, it is a tremendous difference to us.

If you look at our overall budget picture where we have unfunded liabilities of $142 trillion, that is where we are today, 42 percent

greater than the entire net worth of the country, and we can make those kinds of changes, we start seeing some way out. That is why Senator Cruz is calling for this hearing, if we break through on diabetes, if we break through on Alzheimer's, if we break through on all this cancer, we break through on Parkinson's, the cost/benefit ratio is unbelievable to us as taxpayers.

Most of the dollars even with the Affordable Care Act, more and more of the dollars are going through the government, so it is to all our benefits that we have an efficient regulatory process that encourages rather than discourages the development, encourages collaboration rather than discourages it, encourages cooperation, and the assumption has to be we are all in this together, let's see if we cannot get some breakthroughs, and then share it.

Let's change—the other key point—you have to change not only the reimbursement pattern but you have to change the intellectual property so the private capital comes into this.

If you spend 10 years on a drug and your patent is running out, the market is X, you are going to say I am not going to the Phase III trial because here is another $30 million to $50 million going into this drug, and I only have a year and a half left on the patent. They are just not going to do it.

We have to have intellectual property change so we do not stop good stuff, even though Dr. Yamamoto can go back and look at the research if we are collaborative and figure out another way to use that same drug if it is safe.

Senator JOHNSON. Those are my main points. What is going to drive innovation are the benefits and rewards of a free market system. We know that works. The other point is it is the road blocks that Federal Government policies create for those innovators for that free market capital system.

Thank you, Mr. Chairman.

Senator CRUZ. Thank you, Senator Johnson. We are going to do one final round of questioning, and we will thank the witnesses for being here.

In the written testimony, one of the portions I found very interesting, Mr. Huber, was your discussion of very rare diseases, and particularly when overlaid, you describe in your written testimony how with very rare diseases there are often too few patients to conduct a statistically robust double blind trial.

Very rare diseases in the aggregate, according to the National Organization of Rare Disorders, there are roughly 30 million Americans with very rare diseases. In the aggregate, they are not all that rare, even though individually they may be.

Mr. HUBER. It goes even further than that. To begin with, very rare diseases often have a more common variant. One very rare disease drives your cholesterol levels sky high and you die of a heart attack, get this, at 5 years old, it is hypercholesterolemia.

You have statins today because a Japanese researcher found a statin by trial and error, very clever guy, because two U.S. researchers, Brown and Goldstein were working in this country on treating a hypercholoesterolemia patient, and they were able to test the first statin drug in their laboratory. You learn a ton about individual genes, so there are more payoffs than that.

Yes, the very rare diseases, it is just nonsense to even think about prescribing a placebo when testing a drug to treat them, and I might add when these diseases are hereditary, you have incredibly powerful evidence from day one that the disease has a genetic cause and you can identify the molecular mechanism of the disease very quickly.

There is a second factor which I think matters a lot. A lot of these diseases develop very slowly. Genes do not persist if they kill people right away. They have to live long enough to have children and pass on the disease.

Take a drug aimed at one of these diseases to the FDA. By the way, this is very relevant to Alzheimer's, which everybody seems to be interested in, there is an article in the *New England Journal of Medicine,* that I mention in my written testimony that says you simply could not bring an Alzheimer's drug to Washington because by the time given the scientific risks and the risk of not getting through the trials and then the patent clock ticking, no sensible person would do that.

The very rare diseases now, to its credit, the FDA is fairly flexible with very rare diseases. They are willing to take evidence from animals and lab tests and so on.

Once you understand mechanisms, you should be doing that with all diseases. In fact, Dr. Yamamoto and a very distinguished group of other experts wrote the National Research Council report, where they said our whole definition of "disease" is basically antiquated, if you care about drugs and you want to beat diseases with drugs, you have to define diseases by their molecular mechanisms of action, because that is where drugs do their thing.

The day will come and hopefully sooner rather than later we will begin approving drugs by their mechanism of action. You prove that the drug can actually reach down into a body and reasonably safely turn that pathway on or off or disrupt it.

We should license it because certainly in oncology and many other areas, that drug is going to be used wherever that pathway is found. It is just amazingly weird and encouraging that you find the same pathways common to a lot of diseases. This is the cheapest possible drug development process you have. You just take a drug that is already on the market, you find an antidepressant that is suddenly curing cancer.

Thalidomide is a licensed drug today, and actually for 10 different uses, because it turns out it is a cytokine inhibitor. We knew that or we worked it out long after it had been banned, and by the way, it also got to market largely thanks to the HIV and AIDS' challenges of the 1990s. You work out the mechanism of action of the drug, you begin finding it is a cytokine inhibitor. You begin finding cytokine problems in all sorts of other diseases, and Thalidomide is then prescribed for them.

The rare diseases are an opportunity, an important research opportunity, they will pay you twice.

Senator CRUZ. Also, underscoring the human cost. There has been multiple references to the AIDS epidemic and the pressures that came to develop treatments to deal with it.

On the human cost, there was a wonderful movie a couple of years ago, the *Dallas Buyers Club,* which powerfully demonstrated

patients that were being told they could not access potentially life saving medicines in America, so as a result they had to fly overseas to try to save their lives or prolong their lives.

Address for a moment the rights of patients to acquire, to get access to potentially life saving medicines even if there are risks of side effects, if you are facing a certain or near certain death, people will take informed risks. I would be interested in the panel's views on that.

Mr. YAMAMOTO. Let me say something about what is going on at the FDA right now. It turns out the FDA has a tough hill to climb because of the regulations that are imposed on them and the way they operate. There are a lot of smart people there that I think really know the direction they should be moving. They have developed centers of excellence, as Senator Johnson was talking about. There are four of them now, centers of excellence in regulatory science and innovation, CERSIs.

Those groups, among the things they are pushing on, a very strong focus on mechanistic studies that can then be used to move forward in drug development or other kinds of treatments.

There are people within the FDA that understand these things and know the direction they should be moving. They know there is a revolution coming at all of us in devices, things that will measure physiological parameters in the course of our daily lives, and I am wearing one. These things are just the beginning of what is coming to us.

There is also a center for device and radiological health within the FDA that is pushing hard on those.

There is a very good consciousness within that agency of the things that need to be done, and in part, the things that need to be done collaboratively. They do not have the budget or the personnel to be carrying out these mechanistic studies, but they know they have to be done. The centers of excellence are doing these collaborative events within academia.

I think that is the good news. The question is can we make sure we can keep them on pace, look at the regulatory policies that are actually holding them back in being able to move forward, and allow these things to actually come to fruition.

I think that is where the focus of the Federal Government should be. They need and deserve more funding. Commissioner Hamburg, before she left office, liked to point out that the FDA moves at two paces, too fast and too slow. Depending on who the observer is and what the needs are.

Patients should own their data. It is very important. Simply owning their data really has to come with two tools. You just referred to one of them, and that is the ability to have a say about decision-making on being able to utilize drugs. Very, very important part of the risk/benefit assessment that the FDA is increasingly paying attention to, talking to patients.

The second one, of course, is arming patients with the information. Simply handing someone their DNA sequence does not help them very much. We also need to be developing tools, and we are doing this with a precision medicine profile, to be able to inform patients what this vast amount of information means.

Senator CRUZ. Let me ask one final question. Often when it comes to changing the law, we think based on the existing body of law with years of accumulated practices, procedures, rules and regulations, if each of the members of this panel woke up tomorrow, and you were czar for a day, and you could implement one reform at the FDA, in your judgment, what would have the greatest positive impact, facilitating life saving drugs reaching markets and impacting people's lives?

Dr. COBURN. I think changing their charge from safety and efficacy to safety. I think the medical community wants efficacy. I do not think there is any doubt about that. Safety is their number one charge.

I will give you a great example. We now have drug tamper resistant narcotics, but the FDA last year approved another non-tamper resistant narcotic. The question is why. It certainly is not safe. Yet, they say their number one charge is safety and then efficacy.

I think if we emphasize safety and everybody that is working with precision medicine is interested in safety, but lightening up on efficacy because the only way this thing is really going to fly fast in a collaborative fashion is if it is efficacious. That is what they found at UCSF in terms of oat cell carcinoma, and also carcinoid tumors. They found efficacy. They already knew it was safe.

If you emphasize safety and let efficacy go on the basis of trusting your collaborative partners to say this works. We know not everybody is honest. We have seen research work that has been fabricated. That may happen.

The overall benefits tremendously to patients and scientists in this country and physicians is going to far outweigh any bad character actor that you get out there. Most of these people, 99.9 percent of them, are dedicated to helping people. They are not going to falsify data.

Senator CRUZ. Thank you. Senator Peters?

Senator PETERS. Thank you, Mr. Chairman. I just want to follow up and clarify maybe some of the comments, Dr. Yamamoto, you made. I found some of your responses to the Chairman's questions were very interesting and certainly we have heard a great deal about the promise of precision medicine and a number of government reforms, and you talked about some of the work that the FDA is doing right now.

Is the FDA now a fundamental impediment to the next generation of disease preventions, therapies, and cures, or are there other major issues that you think are up there as well, or yes or no, do you see the FDA as the major impediment to us moving forward, and if not, what are some of the other concerns or other things we should be considering as a committee here?

Mr. YAMAMOTO. The FDA is not the major impediment. I suggest that we reorient this question, and instead recognize an opportunity in front of our entire community, whether it is academic researchers doing basic science that leads to CRISPR, or clinicians that are focusing on specific disease, some of them rare and very difficult to study, or investors and companies capitalizing on the tools of precision medicine to link diseases thought initially to be unrelated to each other, and discover there are drugs in one disease area that are very effective in the other.

I think the impediment, perhaps better viewed as an opportunity, is to recognize that by understanding diseases at the level of mechanism, we can more efficiently define and pursue research directions, drug tests and regulatory policies that are much more closely aligned.

To the extent there are FDA policies that presently may impede that pathway, it is a reminder that we all are entering a new frontier, and that we need to recognize across the Government that adjustments and refinements are needed.

Senator PETERS. Dr. Coburn, you talked about the dual mission of the FDA and how should we focus on safety as a primary focus. Yet, I have also heard from the panel some criticisms of the clinical trial process. Would you comment that obviously if we are concerned about safety, clinical trials, are they still an important element of it, and how would you reform that, that does add to delays. What are your thoughts on that?

Dr. COBURN. Thank you. I think it is balance. I think Dr. Yamamoto talked about the trial on a drug that had two deaths. The fact is did we as a society learn something from that. What was the mechanism of those two genetic codes that caused them to succumb when the others did not.

The point is how you look at that. I am not opposed to double blind placebo controlled studies. I am if when we put everything and say it all has to be in this box to prove efficacy because we are already seeing in precision medicine with biomarkers, with massive computer analysis, because we do not need to do that to advance a whole lot of benefit to the American society by going another way.

What you are doing there is talking about drugs that have already been approved for safety, and using them in totally off label usages that have never been approved by the FDA, which I as a physician have the right to do today. If it is approved, I can use it, whether I am smart to do so or not.

Here is the point I would make. If we really want to move forward, what we have to do is change the dynamic at the FDA. Part of the reason the dynamic is there is because of Congress. You beat the crap out of them when something goes wrong, so their underlying statement is never do what is best when you can do what is safe.

I do not blame them. The criticism is so severe. If we change it to where we say we are going to allow a growing opportunity for change within the FDA, change within the medical research community, change within the oncology community, and the physician community, we are going to work some new ways, they are all going to be collaborative, they also are going to be transparent, so we all get to see what does not work, not just a small group.

If you really want that to work, you have to have intellectual property protection and advancement, and you have to not worry about what it costs. You have to measure what it costs based on terms of true cost/benefit analysis, not the sticker shock of some new drug because of what it comes out to.

Mr. HUBER. Can I add one thing about safety? The strongest argument for more FDA involvement is always it takes a long time to expose all the possible side effects, and that is absolutely true.

The FDA has also conceded that the long time is actually infinite time, because there is simply no way to prove a negative. It is always possible the drug just has not yet encountered the patient with the weird biochemical profile who is going to keel over dead as soon as they get the drug.

The FDA therefore relies on doctors to do the hardest safety stuff. There is an international coalition, they gather case reports from all over the world, apparently doctors just observing things can teach the FDA something, too, and they also do the genomic analysis. The FDA set up this whole thing as a global program.

It is exactly what we are advocating, and on the efficacy side, you asked originally, Mr. Chairman, for one sentence, and I do not think you got one sentence from anybody and you are not about to, but I think everybody agrees you want the threshold screening for toxicity and lab tests.

The FDA has actually done a lot of very good work on that. They are increasingly willing to work with cell cultures and other tests of that kind. You want to continue with phase one tests on healthy volunteers to see if these things are immediately toxic. I am not about to volunteer for most of these, but apparently there are people who are willing to.

You have to do that. I do not think most of us propose doing the efficacy by just saying look, every doctor in the country, possibly the world, can have this drug. I think almost everybody would agree we should put these through groups who specialize in these things, and they should be gathering a lot of data, pooling it, making it available.

They should also then play a large role in saying when you are ready to give this larger distribution, but the safety argument is compelling and the FDA has already conceded it cannot do it all.

Senator PETERS. Dr. Yamamoto, final thoughts?

Mr. YAMAMOTO. I am a little bit surprised by Dr. Coburn's comments about guarantees of safety because he also pointed out that as a physician, he can prescribe drugs for off-label use, completely independent of the FDA.

My view is the FDA, perhaps due in part to expectations and sanctions from Congress, or perhaps on their own accord, has perhaps drunk the Kool-Aid that says that FDA approval, "Safety" means there is no chance for anything to go wrong, when they know very well that the Phase II trial, as good as it may be in terms of scientific control, is never large enough, as Dr. Huber pointed out, to rule out the possibility there is some patient out there who may experience an adverse response.

Post-market surveillance is one of the things FDA is increasingly paying attention to. Risk/benefit, I think, is a much clearer metric than the claim of safety. What patients and physicians and the community will sustain depends very much on the weight of risk are against the relief provided by benefits.

Cancer patients are much more willing to take risks on therapies than somebody with poison ivy. Obviously, that is as it should be.

We should really be talking about risk/benefit, acknowledging that nothing is completely safe, and moving toward policies with such standards. The FDA is increasingly doing that, and as I said, including patients, in being able to make that assessment.

Senator PETERS. Thank you. Thank you for your testimony, all of you.

Senator CRUZ. Thank you very much. The hearing record will remain open for two weeks. During that time, Senators are asked to submit any questions for the record, and upon receipt, the witnesses are requested to submit their written answers to the Committee as soon as possible.

With that, I want to thank each of the learned members of this panel. I think this was a very useful, productive and important hearing today. I thank each of you for your time, wisdom and judgment that you brought.

With that, this hearing is now adjourned.

[Whereupon, at 12:01 p.m., the hearing was adjourned.]

A P P E N D I X

Response to Written Questions Submitted by Hon. Steve Daines to Christopher Frangione

Question 1. In your testimony, you mention 30 Federal agencies utilizing smaller prizes, $2,500 to $1 million, to spur innovation. You state that government can utilize monetary prizes as an economically efficient means to incentivize innovation. As you describe, such prizes can be cost effective, reduce risk, and focuses rewards on success. Given the time frame for many research and development projects, how can we ensure that political changes in Congress or the Executive Branch do not have a negative impact on the directive of prizes? Or should these prize structures be left to non-governmental organizations?

Answer. Prizes are good for many reasons. One main benefit is the return on investment. When you grant 1 million dollars you will get 1 million dollars of work. But when you put out a 1 million dollar prize you will get $10+ million in work. We are democratizing innovation. These are things that we have found leaders on both sides of the aisle can agree is good. We at XPRIZE believe that both the public and private sector must work together to see the innovation we want. This partnership can be a powerful tool in solving the most complex problems of today and enhancing the future. As such, we must support policy that enables Federal prizes which is why we support H.R. 1162, "The Science Prize Competitions Act" that amends the Stevenson-Wydler Technology Innovation Act of 1980 to encourage agencies to utilize prize competitions.

Question 2. Our society is faced with many low prevalence diseases which have a high capacity for significant personal and societal loss if there were to be a pandemic, such as Ebola. In your testimony, you discuss how financial prizes often do not cover the full cost of research, rather it is the ability to get a product to market and become a profitable company that is the motivator. How do we create incentives for cures when there is currently no market for a product, but the need for those products could arise at any point?

Answer. As I mentioned in my testimony, incentivized competitions work better in some areas than others. We believe that in the healthcare space, prizes work well under the below conditions:

- Where new forms of cross-disciplinary collaboration are needed;
- Where research is underfunded or there is a small patient pool driving inefficient market activity; and
- Where "engineering" type solutions could bring breakthroughs to bear.

Additionally, what we have found to be critical across all issue areas is the need for an end-market. We know that teams compete primarily for the end market—for the ability to go out into the marketplace and become a profitable company. If little or no market exists, we can try to encourage a market through advanced market commitments. While we know that teams secondarily compete for additional incentives such as marketing, testing, milestone prizes, partnerships and education, that end-market is critical to spur audacious advancements and innovations within a sector.

Response to Written Questions Submitted by Hon. Gary Peters to Christopher Frangione

Topic: Prize Competitions

Question 1. In addition to funding cash prize purses, Federal agencies can provide non-monetary contributions to prize competitions. For example, the Food and Drug Administration is supporting the teams competing in the Qualcomm Tricorder XPRIZE by helping them prepare for post-competition regulatory clearance. Are

there any legal impediments to Federal entities offering "in-kind" contributions or otherwise participating in prize competitions?

Answer. All Federal employees, including the FDA's assisting the Qualcomm Tricorder XPRIZE, must adhere to the Standards of Ethical Conduct for Employees of the Executive Branch. This statute ensures that Federal employees will give impartial treatment to any private organization or individual. President Obama's 2009 executive order, "Strategy for American Innovation", calling for agencies to increase their ability to promote and harness innovation by using policy tools such as prizes and challenges, helps facilitate and encourage public-private partnerships to achieve innovation. In times of question, governmental agencies should seek the advice of counsel, but, in general, Federal employees can be a resource to teams competing for a prize as long as they do not use their position for personal private gain.

Question 2. University researchers appear less likely to participate in prize competitions, perhaps because the prize funding model is not as amenable to sustaining a research lab over a long period of time. What can be done to better tap into the brilliance of our university researchers and to encourage them to compete for innovation prizes?

Answer: Prizes help facilitate collaboration that otherwise would not take place. While university researchers are often engaged in long longitudinal studies, the teams that are competing in our prize competitions are usually focused on an end-market for the product they risk their own money to develop. Grant funded university research provides us with essential early research and discovery in areas we know little about. This research allows us to define challenges and create prizes that incentivize teams around the world to find effective solutions. We can encourage university researchers to be involved in the prize competition process by connecting them with teams and facilitating cross-industry collaboration that leverages research already conducted in a university lab. Prizes can be structured in a way that fosters partnerships between researchers and teams competing for a prize, allowing university researchers to amplify the ultimate impact of the research they have completed.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. AMY KLOBUCHAR TO CHRISTOPHER FRANGIONE

Question 1. Alzheimer's presents one of the toughest medical, economic, and social challenges facing our country. Right now, close to 5.2 million Americans are living with Alzheimer's including nearly 100,000 Minnesotans. These numbers will grow dramatically in the coming years with the aging of the Baby Boomer generation.

Mr. Frangione, by 2050, an estimated 13.5 million Americans will be living with the disease-triple the number of people affected today. In 2015 we will spend $226 billion caring for people with Alzheimer's disease and other dementias. By 2050, these costs will reach $1.1 trillion. In comparison we only invest about $586 million in Alzheimer's research this year. What will be the social and economic impacts of not investing in Alzheimer's research?

Answer. The impacts will be catastrophic and saddening. This is a prevalent disease that needs the attention it deserves. The social and economic costs are rising and affect more people as you mentioned. Of that $226 billion spent to care for people with Alzheimer's, Medicare and Medicaid will spend an estimated $153 billion caring for patients. Roughly one in every five dollars spent by the government on Medicare is related to Alzheimer's treatment. We need to spur innovation and harness ideas from all over the world to find a cure to this disease. XPRIZE supports government efforts to develop an Alzheimer's prize to help address this need.

Question 2. Mr. Frangione, in your testimony you mentioned a prize for Alzheimer's research. Why is it important? How is the XPRIZE model accelerating innovation in comparison to the way the government traditionally funds research?

Answer. As you mentioned, by 2050 an estimated 13.5 million Americans will suffer from the effects of Alzheimer's. That is not the complete picture, families suffer as well, and therefore the number of people negatively affected is significantly higher. We need to respond and take proactive steps to address this ever-growing disease. That is why XPRIZE is exploring an Alzheimer's prize focusing on screening and treatment.

Question 3. I am proud to lead the Muscular Dystrophy Community Assistance, Research and Education (MD CARE) Act with Senator Wicker. The bill supports medical research and policies to boost life expectancy and quality of life for muscular dystrophy patients. I have had the pleasure of touring the Paul and Sheila Wellstone Muscular Dystrophy Center at the University of Minnesota, an institution

that benefits from this legislation and seeing first-hand the critical work they do, particularly to maximize the significant federal, nonprofit, and patient advocacy research funding.

Mr. Frangione, why are public-private partnerships important? Are there other models of public-private partnerships that would have similar benefits and outcomes as the Wellstone Center across other areas of Federal research to explore treatments and cures for other diseases?

Answer. Public-private partnerships are a critical aspect to innovation because they catalyze collaboration that can produce unimaginable technology to help improve lives and to solve complex challenges. President Obama signed an executive order in 2009 calling for agencies to increase innovation by using policy tools such as prizes and challenges. The America COMPETES Act Reauthorization of 2010 gave agencies a clear legal path to use prize competitions in order to bolster their own missions and encouraged agencies to partner with the private sector and nonprofits. Since then numerous agencies and departments have spearheaded prizes that incorporate private and/or public industry partnerships. For example, XPRIZE partnered with the Department of Energy to support a $10 million global competition to inspire a new generation of viable, safe, affordable, and super fuel-efficient vehicles. We brought together government and the private sector, including our lead sponsor Progressive Automotive Insurance. Our top prize-winner, Oliver Kuttner, a commercial real estate developer who loved to tinker with cars since taking auto shop in high school, developed a four-seat, 830-pound vehicle that ran on one-cylinder with an ethanol-fueled internal combustion engine that achieved 102.5 miles per gallon fuel efficiency. Today, Kuttner's company, Edison2, is continuing to develop extremely light, super fuel-efficient vehicles including an electric version.

Public-private partnerships like this have a history of maintaining a commitment to scientific excellence by guiding the conception, safety, and deployment for various technologies that have paved the road to where we are today.

RESPONSE TO WRITTEN QUESTION SUBMITTED BY HON. RON JOHNSON TO PETER W. HUBER

Question. Mr. Huber, you testified that scientists already have the tools that will end up curing/preventing disease and emphasized that every disease Senator Cruz mentioned has a genetic origin. You were optimistic about the array of tools that lets biochemists study the genetic correlations of diseases that might lead to real cures.

In your direct testimony you gave the example of a baby born and tested immediately for BRCA genes which show she is highly likely to get breast cancer in her lifetime and you posed the question of the appropriate place for scientists to begin to intervene. It was just announced that a University of Wisconsin-Carbone Cancer Center scientist will be leading a part of a unique national effort to match cancers to drugs based on their genes and not on where in the body the cancers begin. Dr. Kari Wisinski, a breast cancer oncologist, will lead one arm of the National Cancer Institute's NCI–MATCH trial.

People who enroll in the trial will first have a biopsy of their cancer tissue. Four labs will analyze the cancer cells, looking for 4,000 different variants across 143 genes to figure out which genetic mutation is likely driving their cancer. If the abnormality matches a drug or drug combination that targets that mutation, they will be assigned to that arm of the trial. The trial begins this month. Overall, researchers plan to screen 3,000 people in order to match 1,000 into treatments that target their particular mutation.

Do you think these trials can bring about real progress, and at what point, if ever, should a priority be put on them, in terms of Federal research investment?

Answer. The MATCH trial raises a number of very important issues that have far-reaching implications for the advance precision medicine.

It will certainly serve an important purpose of demonstrating that drugs can be designed to precisely target specific molecular pathways and clinical trials can and should be framed in ways that involve what the FDA currently calls "enrichment" by which it means stacking the deck to prescribe a new drug to patients selected to participate because they present the pathway that the drug was designed to target.

As researchers continue to unravel the molecular pathways that propel diseases that approach should become the norm in the drug-approval process, and Federal funding should be channeled accordingly. Many seemingly common disorders—common as conventionally defined by their clinical symptoms—are in fact clusters of biologically distinct disorders. Their molecular chemistry often varies significantly

across patients. When multiple drugs are then developed to target the different pathways, both patients and drug developers will benefit from trials structured in the same way as the MATCH trial. The patients will be much more likely to receive the treatments they need, and when new as yet unapproved drugs are included in the trials the drug developers will be more likely to get their drugs approved, and approved more quickly and therefore at much lower cost.

Because they are for now a departure from conventional single-drug FDA trials and not currently addressed by any familiar FDA trial protocols it is a good idea that trials of this kind should begin under the supervision of researchers and doctors who have experience and expertise in treating the disease being targeted. Having funded and led much of the research in cancer molecular biology the NCI is an excellent agency to take charge of that.

The scope of the molecular data collection and analysis involved in the NCI–MATCH program is also valuable on its own. Which brings me to a closely related and broader issue that should be addressed as well, and going forward it should receive at least as much Federal funding. As you mention in your question molecular research that spans thousands of variants across 143 genes will be conducted during the course of the MATCH trial. It is quite likely that those analyses will uncover cancer mutations and pathways that aren't currently known, and that aren't targeted by any of the currently approved drugs that will be involved in the MATCH trial.

Ideally, discoveries of that kind would launch the development of new drugs to target those new biomarkers. Those drugs would of course have to undergo clinical trials as well. But they won't perform well in the trials unless tested in patients who present the new targets they are designed to modulate. Which, under current FDA policies, can't happen until the FDA has evaluated and approved the science—qualified the biomarker in FDA jargon—used to link each biomarker to development of a specific clinically defined disorder.

While the FDA recognized the important role that biomarkers should play in the drug-approval process over a decade ago, the Agency has, so far, declined to promulgate substantive evidentiary standards for biomarker qualification. Led by the NIH, experts in the field have been urging the FDA to promulgate such standards for over a decade.

There are now promising signs that the FDA intends to move forward rapidly on that front. Perhaps in response to reform proposals that were being considered by members of Congress involved in drafting the Cures Act senior FDA staffers, analyzed the state of biomarker science at the Agency, assessed the agency's own shortcomings, and published their findings on April 13, 2015 in *Clinical Pharmacology and Therapeutics.* The authors forthrightly acknowledge that while the Agency does have "an important role to play in qualifying potential biomarkers for regulatory use, it does not have all the requisite expertise, resources, or—in the case of inadequate scientific research—the mission, to address these key barriers to biomarker development."

The authors also acknowledge that "while the ultimate decisions regarding qualification of proposed biomarkers currently rest with the FDA, the process could be accelerated if diverse experts and stakeholders came together to identify and prioritize needs, gather relevant scientific information, and develop community consensus in an open and transparent process." An "uber-consortium" of this kind, they suggest, would "conduct substantive reviews and make recommendations to FDA on the sufficiency of data packages developed by industry and public-private partnerships to support qualification of new biomarkers."

Ideally, the NCI and other experts involved in the MATCH trial—experts like Dr. Wisinski and her colleagues, for example—would be involved in framing those disease-specific standards. As noted on the website that describes it the MATCH trial "employs the expertise of the NCI and of specialized investigators and scientists within NCI-Designated Cancer Centers and networks who are at the cutting edge of precision medicine in oncology, as well as clinical oncologist and community practices that are experienced in clinical trials." If the FDA commits to promulgating substantive standards for biomarker qualification and continues to rely on MATCH-like trials overseen by experts from various branches of the NIH further Federal funding of those trials should be a very high priority.

The 21st Century Cures Act, as passed by the House of Representatives on July 10, 2015, does require the Secretary of Health and Human Services (HHS) to consult with external consortia in the promulgation of a FDA guidance on biomarker qualification that includes evidentiary standards. But no single guidance will suffice. Standards will vary based on a biomarker's context of use, the state of the underlying science, and the risks and benefits associated with a given disease state, and the availability of alternative treatments or diagnostics.

Now that the FDA has acknowledged that it cannot go it alone, and that the external scientific community must play a key role in setting evidentiary standards for biomarker qualification, Congress should step in to mandate what the agency itself says is needed. In drafting companion legislation to the Cures Act, the U.S. Senate should include a provision that requires the FDA (with adequate and sustained funding and staffing) to publicly consult with external scientific experts to develop disease-specific evidentiary standards for biomarkers that can be used in the drug-approval process and establish transparent procedures for independent external experts to participate in the process of deciding when the standards have been met.

RESPONSE TO WRITTEN QUESTION SUBMITTED BY HON. RON JOHNSON TO DR. KEITH R. YAMAMOTO

Question. Dr. Yamamoto, in your testimony you noted the substantial need for expanded sustained support for basic research and that Federal funding is a vital part of the research that produces fundamental discoveries. One successful example of this symbiosis could be the University of Wisconsin's trial called NCI–MATCH, which stands for Molecular Analysis for Therapy Choice.

It was co-developed by the National Cancer Institute (NCI), part of the National Institutes of Health, and the ECOG–ACRIN Cancer Research Group. The UW-Carbone Cancer Center is part of the National Clinical Trials Network, a partner in the trials. The trial is for adults with a wide variety of cancers, including some rare cancers, solid tumors and lymphomas. It will soon begin enrolling patients, and will test up to 3,000 people whose cancer has stopped responding to treatment. It is part of the precision-medicine initiative announced by President Barack Obama during his State of the Union address in January.

Given your own experiences, and the precision medicine genomic mapping movement, specifically for cancer, what are your thoughts about the need for a long-term commitment of Federal funding for precision medicine programs?

Answer. Thank you, Senator Johnson, for this thoughtful question. It is exciting that your outstanding research institution, the University of Wisconsin, home to many superb investigators (including many of my close friends), is playing a key role in the President's Precision Medicine Initiative through its leadership of the NCI–MATCH trial. As you know, clinical trials are essential for collecting and organizing observational data, and for rigorous testing of therapeutic drug and device candidates.

The findings that suggest and enable these trials, including UW's 3000 patient NCI–MATCH trial, arise from fundamental discoveries about biological processes—the outcomes of basic research. And as you also know, neither basic research nor the full three-phase clinical trial process, both critical steps for precision medicine, can be carried out on predefined schedules. Thus, it is the "long-term commitment of Federal funding for precision medicine programs", supporting and extending President Obama's Initiative, that will truly motivate researchers and clinicians to team up and carry out this important work.

RESPONSE TO WRITTEN QUESTION SUBMITTED BY HON. STEVE DAINES TO DR. KEITH R. YAMAMOTO

Question. In my home state of Montana, we have the Rocky Montana Laboratories (RML) operating under the National Institute for Allergies and Infectious Diseases in Hamilton. This is one of the few biosafety level (BSL) 4 labs in the United States. The Lab employees 450 locally, but it contributes globally with its research on contagious diseases such as Rocky Mountain spotted fever, Q fever, and Lyme disease.

Based on your experiences at University of California, San Francisco (UCSF), how would adding a financial incentive change the dynamic of research being conducted at a public facility under the purview of the National Institute of Health, such as RML?

Answer. Thank you, Senator Daines, for your insightful query. RML is world-renowned for the many important research projects carried out in its laboratories. My friend Dr. Stanley Falkow of Stanford University in the San Francisco Bay Area, who is described by Wikipedia as "the father of molecular microbial pathogenesis, which is the study of how infectious microbes and host cells interact to cause disease", was a Hamilton resident for many summers before his retirement, carried out research at RML that has had enormous impact on public health world-wide, and continues to consult with RML microbiologists.

I can say with certainty, based on my 40 years as an NIH-funded researcher at UCSF, and as in my role as Vice Chancellor for Research there, that it is the potential for Federal funding, especially from NIH but also from other Federal agencies, that has incentivized and enabled remarkable research studies at UCSF, RML and ~1700 other institutions in all 50 states. This is an investment of Federal dollars that has truly had, and continues to have, a spectacular impact. At this time, when the Federal budget is so limited that only about one in ten NIH grant applications to carry out microbiological research can be funded, there is absolutely no doubt that additional support would increase both the motivation and the productivity and impact of research being carried out at all of these institutions.

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