

National Health Research Forum

Michael Coburn:

Good morning. Thank you. Good morning and welcome to Research!America's National Health Research Forum. I'm Mike Coburn, Executive Vice President of Research!America. I'm stepping in for Mary Woolley, Research!America's CEO, who today is with her daughter and newborn baby boy in New York.

[applause]

And I'll let Mary know we applauded it. Mary regrets that she's not with us today, but sends her very best wishes, and of course we wish she and the family very well. On behalf of our Board of Directors, and if you're here, please waive so we can acknowledge you -- and on behalf of my great colleagues on our staff, I thank you for being here today. Those of you who are not in the room, and joining us via WebLink, we thank you for being with us, courtesy of WebMD.

Our annual straight talk program is intended to get your juices flowing with ideas, comments, and questions about the future of medical and health research and innovation. Today, being only two months from election day, the uncertainty in the air will no doubt be reflected by our panelists. What can we expect with a new president and a new Congress? Research and innovation already operates with one hand tied behind its back, given the inadequate appropriations to our federal agencies, and absent or outdated policies holding back innovation.

And on top of that, we have a stand-off in Congress. Zika funding, 21st Century Cures, and potentially a continuing resolution to fund our government are issues that may not be resolved in this year. And yet there is so much at stake. Failure to respond to a public health emergency, failing to achieve the hopes and expectations of patients, failing to attract and nurture the next generation of scientists and innovators, failure to speed the pace at which new life-saving technologies are developed. So if you know Research!America, and many of you do, or actually most of you do -- and thank you for your memberships -- we are actively advocating in Congress right now for action this month.

Meanwhile, we're not letting grass grow under our feet with regards to the upcoming election, and along with our partners, many of whom are in this room, we are hard at work with our voter education program, Campaign for Cures, which we launched exactly one year ago here. Today we have more than 400 statements from candidates running for national office on our website. It's worth checking out. There's a card on the table that has a Q.R. code that will direct you to the website and the link.

I urge you all, if you haven't already, to engage with your candidates and ask them what they will do to support medical progress. Research!America is also informing this election season by releasing a new report on U.S. investments in research and development, and here are a few preview -- here's a preview of the findings. Investments from government; academia; industry; voluntary; health groups; professional societies; and foundations in research and development has been constant to increasing over the last few years, with industry leading the way and accounting for 65% of the U.S. investment in 2015 -- more than any other sector.

But growth has not been uniform across all sectors, and our nation is spending less than five cents of each health dollar on R&D. So the outlook for R&D investments remains highly uncertain, and this is

not time to be complacent in our advocacy. Please watch for the release of our investment report in the coming week.

Before I begin the program today, I would like to extend our special thanks to our sponsors, who have helped make this forum possible. Our lead sponsor, Janssen Pharmaceutical Companies of Johnson and Johnson; panel sponsors AdvaMed and Amgen; B.D.; Elsevier; PCORI; our topic sponsor Astellas; science sponsors Bristol-Myers Squibb, GlaxoSmithKline, Sanofi, Takeda, and UCB; and of course our media sponsors, C.Q. Roll Call, and WebMD, which is hosting today's live stream to viewers across the country. Thank you all so very much.

Now I'd like to introduce our Keynote speaker, Dr. William Hait, who is Global Head of Janssen Research and Development, one of Janssen Pharmaceutical Companies of Johnson and Johnson, and a Research!America board member. And we're pleased to partner with Bill earlier this year, with another one of our board members, Dr. Keith Yamamoto, who is Vice Chancellor for Science Policy and Strategy, and Vice Dean for Research at the Medical School at University of California, San Francisco. Bill and Keith did a session at the BIO International Conference on a concept that Bill has coined, "immorbidity," and he'll explain more in his remarks today. So it is truly a pleasure to welcome our friend Bill Hait to the podium.

[applause]

William Hait:

Thanks Mike. It's good to be here. Flew in on the red eye last night after a whirlwind trip, so if I doze off, just kick the podium or something.

[laughter]

But it is a very important moment. It is a moment of -- I would call national consternation. The teetering on the precipice of a disaster, in case you haven't been watching CNN, and one of unprecedented urgency. And by the way, there's also an upcoming presidential election.

[laughter]

Biomedical Research Enterprise, which underpins the health of our nation and much of the world, is in dire need of substantial, substantial transfusion to meet the great medical needs of our times. From Ebola to Zika, cancer to Alzheimer's, diabetes to congestive failure -- but while we await someone to take action to improve funding of biomedical research, we are losing precious time. Some of us can remember a time when no career was more attractive or exciting than a career in medicine -- when medical research carried out by curious physician scientists was American medicine's highest calling, and whose output built the biotechnology industry and sustained the pharmaceutical industry. Yet somewhere, somewhere along the way, it seems that we've lost our way. The time is right to renew our commitment to this endeavor.

Today, the pace of scientific discovery boggles the mind from a time when cloning and sequencing a single gene could take months to years, to today, when decoding the entire human genome can be accomplished in a day. And some new technologies will have it done on a chip that you can actually insert into your P.C. to get the read-out. The time when our ability to translate scientific discoveries and benefits for patients is breathtaking. Today, most of us can know all the diseases to which we are susceptible. We can measure our risk and monitor our progression down the pathway to illness.

I hate to say it, but all of us are incubating some awful disease. At each step along this journey, there will be unimagined opportunities to develop solutions that will interrupt the disease-causing process, and this interruption of a disease-causing process will shape the future of healthcare. The unprecedented pace of change threatens to cloud our ability to appreciate or fully envision what the future of healthcare will bring.

So what J&J did this year, we convened a diverse group of talent people from across our sectors, to envision healthcare 2030, and to begin to understand what we would have to do today, to make that vision for tomorrow a reality. The output was astonishing. We concluded that today, our cars get better healthcare than do we. Where automobiles are embedded with numerous sensors that monitor the function of each component-part, and when a rolls off the assembly line, its normal specifications are known, and if there's a discursion, the check engine light illuminates.

And I don't know about you -- it's so annoying, you have to do something. And this signals that it's time to download the data to a computer, to make an adjustment before something goes wrong. By 2030 we'll begin to resemble our cars. We too will be embedded with wearables, implantables -- all sorts of sensors that will know our specifications when we roll off the assembly line. The women at J &J hate it when I say that, by the way.

[laughter]

And our check engine light will illuminate if we fall out of spec. Data from our sensors will then be downloaded into a watts and light computer, and we will receive instruction to make lifestyle changes, adjust our medications, or in some instances, see a healthcare provider, and do something to intercept a disease-causing process. So in this future state, we'll move from managing disease to preventing diseases before they occur.

We have termed this future state "immorbidity" -- living life free of disease, and knowing it. We've embarked on a journey of substantial change, where discovering and developing drugs that treat the manifestations of disease will no longer be acceptable. We'll evolve to predicting and preempting the disease before illness ever occurs, and if that fails, we should concentrate on nothing short but curing a disease -- for that's how we envision, one disease at a time, a world without disease.

This fits nicely into the values of the J&J credo, where our first responsibility is to the customers who use our products. No patients want a disease so they can be treated. Let me give you an example. I had the privilege of taking care of our oncology patients for almost 30 years. Not once did I hear "Dr. Hait, I am so glad that I've been diagnosed with cancer so you can treat me." Instead I more often heard "I never smoked. I never drank. What could I have done to prevent this awful thing from happening?" Last spring, my 15-year-old daughter came home from boarding school, and asked me what I was working on. When I said "a world without disease," she responded without hesitation, "Well that's impossible." So I sat down with her to share this piece of history.

Over 50 years ago in a football stadium at Rice University, President Kennedy challenged this nation to go to the moon, and he did not minimize the difficulties to be faced. Let me tell you a few of the things he said. He said "we shall send to the moon, 240,000 miles away, from a control station in Houston, a giant rocket longer than the Rice football field, made of new metal alloys -- some have not yet been invented -- capable of withstanding heat and stresses several more times than have ever been experienced. These pieces will be fitted together with a precision better than the finest Swiss watch,

carrying all equipment needed for propulsion, guidance, control, communication, food, and survival -- on an untried mission to an unknown celestial body, then return it safely to Earth, reentering the atmosphere at speeds greater than 25,000 miles per hour, causing heat about half the temperature of the sun -- and do it before this decade is out.” He knew that some would feel that this adventure would be impossible, that we should keep our feet firmly on the ground, do what we know how to do, and do it over and over again. On July 16, 1969, that giant rocket Apollo 19 was launched from Cape Canaveral, and on July 20, Neil Armstrong set foot on the moon.

What drove the space mission was not scientific curiosity alone, but also the threat of Soviet domination of space for military advantage. Today, we in Biomedical Research also face existential threats. Some of our nation's leaders fail to get it, fail to see the importance of investing adequately in our research institutions, where the fundamental discoveries that underpin products that improve human health are made.

Our biopharmaceutical model is probably also not sustainable. To bring a single drug to market today requires an investment of almost two billion dollars. Prices that society is willing to pay for our products are decreasing, and in some cases, decreasing to the point where the enterprise may no longer be viable. Competition is intense, regulatory hurdles are high, and our industry is ripe for disruption. Yet most companies continue down the same road, hoping to slip one more in under the finish line before the proverbial other shoe falls, and price controls are forced on us. And yet we believe that great companies like Johnson and Johnson will be around forever. But other well-known companies have felt the same way, and they are gone.

So we can strive to do great things. We can choose to prevent, intercept, and cure. We can choose the extraordinary over the ordinary. We can think differently. We can attempt to create a world without disease -- and to overcome resistance to change, we recall the words of our company's founder, Dr. Paul Janssen, who said, “The human mind is like a parachute. It works best when open.”

[laughter]

Let me conclude by thanking Research!America for inviting me today -- it's our honor to be hosting this luncheon -- and for this organization's tireless efforts to ensure, through research funding, a healthier future for us all. Thank you.

[applause]

Michael Coburn:

Thank you Bill. We appreciate your remarks today, and again, thank you and the Janssen and Johnson and Johnson organizations for serving as lead sponsor. Now we'll turn to our first panel of the afternoon.

Our moderator is Nsikan Akpan, and Nsikan is the Digital Science Producer for PBS Newshour. He is co-creator of ScienceScope, a video series that explores the ins and outs of basic research and innovation. Prior to joining Newshour, his work appeared on NPR, Science Magazine, Science News, Scientific American, Newsweek, and elsewhere. We're delighted to have Nsikan with us today.

Our panelists are Dr. France Cordova, who is Director of the National Science Foundation; Dr. John Danaher, President of Elsevier Education; Donna Cryer, who is CEO and President of the Global Liver Institute; Al Lauritano, who is Director of Strategic Technology Partnerships at B.D.; Dr. Keith

Yamamoto, who is with UCSF, who I mentioned earlier; and Dr. Anthony Fauci, Director of the National Institutes of Allergy and Infectious Diseases, who is pleased to be with us for part of the discussion today -- but we understand Capitol Hill beckons, and may have to leave a little bit early, and we understand that. Thank you.

Nsikan Akpan:

So I just want to start by saying thank you to Research!America for this opportunity to moderate this distinguished panel. Most of these people were making significant advances to science, health, and medicine long before I was in Pampers, so I feel very honored to be up here right now. If you hadn't heard, it is an election year, and so I'm excited to spend the next hour talking about taking stock and looking ahead.

The plan is to chat for about 50 minutes about the evolution of health research, or research funding in general; the emergence of technologies like CRISPR; the future of healthcare delivery for patients; and the roles for research stakeholders. And then we'll take about 10 minutes to field questions from the audience. So let's start with national research priorities and President Obama.

Over the last eight years, his administration has launched a number of initiatives related to research, health, and medicine. These programs cover everything from the brain to the microbiome. So, I have a two-part question. How much progress do we as a nation, in the scientific community, have to show from these initiatives? And if you had been POTUS, what would you have done differently? Is there an initiative that you would have started, changed, or tweaked?

And I actually want to start with Dr. Fauci, and then we can move down the line.

[laughter]

Anthony Fauci:

So you want to ask me if I would have done anything different than the President did?

[laughter]

Nsikan Akpan:

That is correct.

Anthony Fauci:

So let me just make a couple of comments about -- I think initiatives are really very important, because they really stimulate activity that sometimes smoulders around, but doesn't really essentially concretize and come together in an initiative that really galvanizes people to really push the envelope in various areas. One of the problems that we have been facing with, in biomedical research, is that we've been dealing with a flat budget, essentially for the last -- oh 13 or more years. You know, all of -- and I see people in the room who were around when we had the doubling of the NIH budget from 1998 to 2003 -- and then variably speaking, from 2003 until the present time, except for last year, we essentially had no increase.

So it's very difficult to make a balance of initiatives, which are needed, with a support for undifferentiated biomedical research -- which serves as the incubator for the initiatives that you're talking about. So what I would think in the future -- and this is what Research!America is essentially all about -- is advocating for biomedical research that, looking forward, we have a balance between

initiatives that we essentially designate as an initiative, and the fundamental [unintelligible] biomedical research that'll be the basis for initiatives that'll come along later.

So I have a bit of a concern -- maybe that's not a popular concern, but I have a bit of a concern when all that we have is initiatives, and we don't have a situation where there's enough basic biomedical research to be able to be the incubators for initiatives of the future. So my feeling would be that I think we've done as well as we could have done, on the very, very serious budgetary constraints, but looking forward I would like to see that delicate balance between initiatives and the undifferentiated research that is so important to what we do.

Nsikan Akpan:
Dr. Yamamoto?

Keith Yamamoto:

I don't differ from what Tony said, but I think that I come at it from a slightly different angle. And that is that I -- you know, echoing Bill Hait's comments about Kennedy's challenge to go to the moon. I think that if the challenges are important, and they are broadly framed -- framed broadly enough that they actually include the full range of research, that will intrigue the basic scientists as well as the clinicians, as well as the social and behavioral scientists -- as well as the people who are not thought of as traditionally being involved in biomedical research, in the case that we're talking about -- to get involved. Then, I think that what Presidential initiatives, federal initiatives can do, is to broaden the tent, and intrigue others to get involved.

And I think that's what happened, clearly, with the challenge to go to the moon. At the time, it was very clear that the technologies were not available to be able to do that. The Human Genome Project, the technologies to sequence the human genome were not available. But in fact, the challenges were laid out in such a way that it intrigued those who thought they could get involved, could contribute in some way, and add to the possibilities eventually being able to achieve, to meet the challenge.

I think that initiatives like that, that are framed in that broad way, could actually broaden the tent, and I think that's what can really serve well. I don't have any particular view that I would have launched different initiatives than the President has. I think that we're very fortunate that we have an administration that thinks about science and, in particular, about health, in a way that he wants to be able to make this a part of his legacy, and be able to contribute in a broad way across society.

So I think we're fortunate, and I think that the initiatives that have been enunciated so far are actually of the sort that I'm talking about -- that are broad enough that fundamentally curiosity-driven scientists can think of ways that they can do something in their realm, pursuing their interests, that can contribute. So hopefully that -- I'm hopeful that that sort of thing will continue as we move into the next administration. I think that such efforts will bring -- trans-disciplinary research will bring in people from other areas, will intrigue scientists across the board, both within and outside of biomedical health, and will get the public involved, because they will be able to -- if well-enunciated, the challenges will be those that identify with them as well.

And so patients and people who don't want to be patients can find ways to be involved as well, and I think that broadening the tent in this way is really important.

Nsikan Akpan:
Mr. Lauritano, how do you approach this from a biotech angle and drug development angle?

Albert Lauritano:

So first, before I address that, I'd just like to ask -- is anybody in the room here from Google? Microsoft? IBM? Apple? It's a trend. So my responsibilities at the company -- and I've been very fortunate, to kind of work on the very -- what we call the "front end" of innovation. The front-front end, so even before ideas are being crystallized, and seeing where the trends are going.

And what I've found over the last two and a half years of doing this, is that there's a whole group of people out there in the tech world, that they don't know who I am. They don't know who my company is. They may not know many of you. They don't come out of medical schools, but they're going to challenge -- they're going to solve the world's problems.

Now will they? I don't know. Maybe some of them will, but I think what's going to happen is they're going to bring some fresh ideas to the mix. So I think this whole issue of sourcing the crowd, bringing other people in here -- so what I do is I create partnerships. I leverage what people can do best, and bring them into an early stage, to kind of create something new.

We work with a lot of accelerators around the world, and one of our key programs is -- what we're trying to do is take that, bring that start-up model in-house, because there's so much technology that's out there. The technology's happening, at least on the digital space. We just don't know what to do with it all. It's really how you deploy that technology. What are the business models around that technology? Those are really more of the challenging areas for me, working at B.D. and also being concerned with the overall -- providing better healthcare within our country. So -- and the world.

So I just think to be able to mobilize those folks -- we also have a program at Singularity University, if any of you have heard of that, which addresses big global challenges, and takes them from a very different set of ideas, and doing design sprints around this. You know, what I've seen people create in a matter of 10 weeks is just simply amazing. But they have to be kind of given permission, many people, especially in a corporate world, to do that.

We've been fortunate that in putting a small start-up team out there on the West coast -- you know, heart of Silicon Valley -- and really saying, you know, "don't use the rules that we use within a big company." I mean I think the comments that the gentleman from J and J said earlier, I mean, were right on. But it's not just a matter of taking technology. It's really a matter of thinking differently, doing things differently, and believing -- allowing to fail, and -- because some of these are going to take hold.

Nsikan Akpan:

Miss Cryer, how do patients and patient advocates approach these initiatives?

Donna Cryer:

Well I think we approach them in ways that we just discussed. So much of what Dr. Hait was mentioning in his remarks is really the world that I live in now, as a patient advocate and as the leader of a patient advocacy organization. As you can see I'm, you know, wired and wearable already -- and it was the reason that we created the Global Liver Institute as an innovation and collaboration hub, not as something [inaudible] necessarily new initiatives or programs. And so when I think about not only the question you just posed me, but the questions that have been posed, and look back across the past eight years of this administration, we've seen fabulous initiatives that give a sense of excitement for those from the patient community, and I do have IBM on my board. We have been out to Apple and to

Google. I know organizations like the American Heart Association has a very large investment and program with Google with Verily, so I think the patient advocacy programs, those who have the urgency of the everyday -- of how do we solve the problem for me right now.

We have been seeking those novel approaches and those novel ideas, and I think that in taking stock -- you know I went back and spent a few days re-reading a lot of the books that most of us are mentioned in, or referenced in, or helped write, whether thereby Dr. Emmanuel or Senator Daschle, or Steven Brill, or now Daniel Dawes, and those are now becoming history books. I know it's a strange thought, because it's the times that we have lived through. So I think in terms, not so much individual initiatives, but how are we going to bake in the new principles and the ways of working that we've created over these eight years, and those principals, first and foremost, have been about involving patients and patient advocates, and patient advocacy organizations, three different things I would mention in novel ways, in ways where we're not seen just as the beneficiaries of care but as the stewards of innovation and as partners and peers in not only entering into clinical trials but designing the trials and of identifying the problems as well as helping the solutions. So I think that what we need to take stock of and what we need to make sure happens in the next few months is that the ways of collaboration, the methods of data-driven prioritization, rather than who has the loudest voice, or who has the biggest lobby, but what has the greatest impact on our public health, and what has the greatest impact on our overall productivity and health as a nation and health as an economy needs to be what's driving the frameworks and the principles for how we continue to move forward.

Nsikan Akpan:

Okay. And then Dr. Danaher, how does the education sector and also the publishing sector approach the initiative?

John Danaher:

Sure. And I'll go back to the initial question about "have we made the right bets, etc.". So I'm from Elsevier. Many of you know us from our publications--Lancet, Insel, and from our textbooks, Brunwall and Netters [spelled phonetically], etc.--and we also provide decision support tools to researchers, to scientists, to clinicians, science [unintelligible], etc. 25 years ago, I had the privilege of working for Dr. Sullivan at HHS, and we were asking these same questions. Were we making the right bets? And how could we make the national research agenda less reactive, more proactive, and how could we ensure that it wasn't affected by the political process, and how could we make sure that funding was robust and continued strongly going forward? And it was a very political time. Dr. Fauci led the leaders coming to advocate and to champion funding for HIV research and AIDS, and what I realized then, and what I think we realized then is, that it was less about, were we picking the right initiatives--clearly, there were some things we had to fund, and it was more about how do we ensure that our nation's research agenda could be understood by the American people, and how could we make sure we demonstrated those metrics of success?

And so what I would say is there are lots of opportunities going forward. I think, whether we fund Alzheimer's research, or we fund the Cancer Moonshot, the opportunities for us going forward is that the Affordable Care Act has changed the financing of our system, so our focus now will be less episodic, more longitudinal. The Affordable Care Act will have an impact, in my opinion, upon basic research, about clinical research, about health services research, and it's going to -- as you know, a central tenant of the Affordable Care Act, patient engagement/patient involvement. And I believe those changes will allow us to engage the American public in a meaningful discussion about their health both for chronic conditions and chronic diseases but also in the pursuit of wellness and to have them participate in understanding our research priorities and where the funding is going. So those would be

how I would respond to your initial question of “have we made the right bets and have we done the right things”.

Nsikan Akpan:

Great. Great. Thank you. Dr. Cordova, NSF has benefitted mightily from many of these initiatives. How do you view them, and would you change any of them?

France Cordova:

We’ve been really thrilled to be a part of the precedents and the White House’s initiatives on things like the brain initiative, the Cancer Moonshot, advanced manufacturing, and so on. And what we’ve learned by being an engaged partner is just how important partnerships are in all of this especially in the times of really tight budgets. And I would say, in my experience, there’s not been a time that like the present in which the word “partnerships” has taken on a new meaning. It’s not about a superficial just doing the same things, but in different ways among various organizations, but it’s about real, true engagement and looking at what are your unique strengths as a private foundation or a federal agency or research institute, and what can you uniquely contribute to these grant challenges? And so that’s, I think, leveraged what we can do in times of really tight funding, so that’s one thing I’ve learned, and the other is that -- so we’ve taken a queue from the White House’s big initiatives, and we’ve looked at our own agency -- National Science Foundation funds all of science and engineering except for biomedical research directly, but indirectly we do a lot of biology research -- and where are the holes, what are the gaps? What kind of big initiatives can we foresee that we’re already funding at a lower level, but need to go to the next level?

So we’ve identified 10 big ideas for future investment, six of those are research areas that are really ripe for investment, and four, interestingly, are process ideas, big ideas, because as a federal agency, what you’re really trying to do is figure out where your investments should be made. Where’s the best place, because we’re not doing the research ourselves. It’s everybody out there that’s got the great ideas. And how do we get more great ideas to take off and really go to the next level? And what are we doing now that’s actually hindering or putting obstacles in the way of those going to the next level? So four of our big ideas are actually how to change as a federal agency and adopt wholly new practices. I’ll just mention one, and that’s because it’s probably familiar to everybody in this room, and that’s the idea of convergence. Recently MIT rolled out a big convergence plan at the National Academies on health and how to bring together all the disciplines to attack health in new and novel ways. And so we’ve taken a page from that, and were trying to apply the theme of convergence and coming together in new ways to everything we do -- to all of science of engineering. So I think that, as was started by Tony and then all the way up through the line, that these big initiatives have encouraged us to think in new ways, and that’s arguably -- I mean the goals are very important, but also the process and the approach is how you get there is equally important.

Nsikan Akpan:

Perfect, and so I think each of you touched on funding gaps, and I actually want to circle back to Dr. Fauci. So the past four or five years we’ve had major, international outbreaks of infectious disease-- Ebola, Zika. What gaps do you see in terms of research and development for drugs in those emergency situations?

Anthony Fauci:

Well, that’s a question that we’re struggling with right now, and I think it’s important, because many of us, myself included, and Tom Frieden has spoken about that and others, about the need to not have to rely on the standard appropriations process when you need to respond to an emergency situation. I

think -- I can't imagine anybody in the room has not been following the most extraordinary experience we're going through, which is we're trying to address a pandemic that's unfolding in front us, and we don't have any resources for it, and what's evolving now is just really extraordinary, where we're taking money from other accounts. If you look at just the NIH and the CDC as in exactly the same boat, when we made a decision, which was a good decision, that we were going to address in a very aggressive way the unfolding Zika outbreak, we decided that we needed to do certain things.

The NIH had to do a few things, but one of the most important was the development of a vaccine. The CDC had to do things in the public health arena of partnering with the state and local health authorities. We didn't have any money, so we took money from other accounts. I took money from accounts that I was going to spend in the summer -- Malaria, Tuberculosis, Influenza -- and I got to a certain point where we went to the pre-clinical in the vaccine, and then I had to start a phase one vaccine, which we did on August the 2nd. So I didn't have any money, so Secretary Burwell transferred Ebola funds to the tune of forty-seven million to allow me to start a phase one trial. When you start a phase one trial, then you have to go in and prepare the sites for a phase two trial, and in order to do that, you need money. So we didn't have any money. So then she had to do something, which was very painful for her -- she had to take money away from cancer, heart disease, diabetes, and mental health -- to give me money to prepare the sites for the phase two trials that we're going to start in January/February. So now it's September.

We're running out of the fiscal year, and unless we get an appropriation for the fiscal year which begins in a few weeks, I'm going to have to do the unthinkable. I'm going to have to stop the vaccine trial endeavor, which is, I think, historically unprecedented. So if you're asking me what the gaps are, the gaps are that we have a broken process that doesn't allow us to respond to emergency situations, whether the solution is to have an emergency public health fund so that she can go and tap it immediately to do the things that we have to do as opposed to getting involved in appropriation process, which when it works right, it can be very efficient, but when you get political aspects involved with it, it essentially stops on a dime, and nothing happens, so I think what we're experiencing right now should be a lesson for all of us that what we're going through right now in our response to Zika is just really unconscionable, but it's happening.

Nsikan Akpan:

Right. Miss Cryer, you wanted to follow up?

Donna Cryer:

I just wanted to say that -- to reinforce Dr. Fauci's point -- to making our health leaders jump through hoops to respond to emergency after emergency is truly unconscionable, but when I think about how we look forward to really think about where the funding allocation should go, where the gaps truly exist, we haven't made investments in two areas that are crucial. One is in surveillance, so we don't really have a handle on what problems we have as a nation in terms of our health. So, making effective decisions about allocations of funds is based on insufficient data, to put it lightly. The second lack of investment that we have made is a lack of investment in predictive analytics, so we haven't used the data that we have to really project and to look forward and to see where our investments will make the biggest impact not only where they should have been yesterday, but where they need to be today, tomorrow, 10, and twenty years from now. And I think if those were two concerns and two priorities that we would do a better job, and I think folks -- like Tony's job would be a little bit easier.

Nsikan Akpan:

Is it just up to public funders to create these emergency funds, or does the private sector play any --

Donna Cryer:

Not at all. I think that the most exciting thing would be creating not only you know the partnerships that Dr. Cordova talked about so much and that were mentioned among large companies and that we see in this room, but really creating an entrepreneurial ecosystem. We can't crowd fund our way out of this, but I think that really utilizing everyone's talents and small companies, large companies, looking at advocacy organizations differently who are now, through faster cures and through other things, funding research as well and looking at all players, all hands on deck. And thinking about funding partners in new ways is an important aspect as well.

John Danaher:

I would just comment on Dr. Fauci's comments. I came to Washington twenty-five years ago believing that social policy drove the national research agenda and health policy decisions, and I left believing that economics and finance in the political process is what is really dictates it. And I say it to you because going, harkening back twenty-five years ago in the time of Act Up and HIV research etc., not having frameworks and to be able to think through and gain consensus about how much do you fund breast cancer research, how much do you fund AIDS research, how much do you put as a rainy day fund for Zika or for Ebola, etc.-- and that as much as that ability for the government to do cost-benefit analysis, cost effective analysis, etc., and to have a structured way of doing it, I think, is one of the reasons we run into these problems. You know to a certain extent you can never have enough money when a crisis occurs, but I think the absence of those decision making frameworks was something, I think, I was very much struck by. And then the absence becomes very political.

Male Speaker:

Let me talk about a funding gap at the other end of the spectrum completely. I think responding to crisis and urgent needs is really important, but there's another end of that spectrum, and that is stability in funding. For the fundamental research to go forward requires a public statement and support for risky research, research that has a reasonable chance for failure, but if successful can really have a big impact. We know so little about biological processes and therefore disease processes that we have to maintain that strong base of basic research in the way that Toni started talking about it in his first comment, and to do that requires a recognition that fundamental research, curiosity-driven research, higher risk research does not operate on an annual calendar or over a quarter calendar. And so really it is the federal government that must support that kind of work. The private sector can't support it at that level, and in recognizing that it doesn't operate on an annual calendar the way that the federal budget does, there has to be some thought given to being able to assure the basic scientists that are pursuing those questions that their funding will be sustainable. And thinking about that in a new way is something that I think would serve the process very, very well. To be able to give that kind of assurance that the federal government and the public are placing that kind of trust in the really high innovation scientists across the spectrum, whether it's technology or molecular biology or health services across the board, it will make a huge difference in the ability to advance that kind of work.

Albert Lauritano:

The issues around budget are certainly not isolated to the public sector. We're right in the middle of budget season right now, so I know these challenges as far as being able to maintain funding for innovation type activities, but one of the adds I'd just like to make to some of these issues is the value of data. And I don't want to overlook that is that so much is going on right now. So many companies are investing dollars purely for the data to come back, and I've been interested too to find out that some of the organizations are very reluctant to share data. They think they have the very valuable resource. So I think unless they have some ways and maybe some new models and stuff to stimulate some of this

data sharing, I mean I think--I don't want to say the answers are out there--but certainly if we're able to pool data from multiple healthcare systems, it's going to get us much closer to an answer than it is to just look at each isolated system. And I've seen that with IBM Watson in some of their customers. They don't share across. They want IBM Watson for their population, but it's not working across the system, so it's -- I think there's a lot of value there. I think there's things that we could mine from the data that could create value and business opportunities that we haven't even started thinking about, but I agree with you that there's need to be some kind of more entrepreneurial, public-private partnership early on and not consortiums where people are all kind of arguing about who's in control, but really much more take an initiative and give everybody their action and their piece of ownership in that and then let them actually do something.

Nsikan Akpan:
Dr. Cordova?

France Cordova:

Yeah, well, Al's point is one that Vice President Biden and the president himself has spoken passionately about the idea that approaching the Cancer Moonshot by sharing data as one of the big themes of that initiative. And I think that's one of the other remarkable things about our time. That is within our grasp of being able to do that, and the whole real challenge is how to do it and the commitment to do it and to do it very well. There's another gap, since you asked about gaps, that is relevant to the folks here interested in and passionate about healthcare but to every domain of science technology, and that's the whole STEM workforce and the education gap in this country, which you just read about and can see the statistics everywhere on this. And the National Science Foundation is very much engaged not only investing in fundamental research but in the STEM workforce and in STEM education. And this is something that private entities are also just increasingly becoming aware of and committing resources to, and I think there's a real opportunity here to figure out who does what, and universities are, of course, changing their approaches.

We have all -- I'll just mention one initiative. It's called NSF INCLUDES. INCLUDES is an acronym, and it's all about broadening participation, engaging more women and minorities in STEM fields broadly from k-12 and all the way up through university and beyond to the CEOs of corporations. And how do we do that? Well, one agency can only invest kind of pilot money in innovative ideas, so what we've done is invite the whole country to submit their most innovative approaches. Again, looking for what haven't we thought about before. Why haven't we moved the needle? What kind of new thinking do we need to get to really broaden participation? And we had kind of a month-long time scale for proposals. We got 600 proposals from around the country with people like university presidents and heads of research institutes being the PIs on these. We could only select about forty of them, and we just are naming the winners right now as pilot programs, but I think it's that kind of engagement on some of these gaps of figuring out -- I mean, there's a lot more innovation and creativity out there than there is in any one of our organizations, and how do we tap into that effectively and then fund that and see where it goes and how does it scale.

John Danaher:

Those are two areas -- there's a little bit of a gratuitous comment -- but those are two areas that we at Elsevier are very, very passionate about: the concerns about STEM education and the people going into research and the significant supply and demand and balance between nurses and doctors and health professions and what we need to provide for care, and then the other one is obviously is the promise for big data in terms of unlocking and enhancing everything from precision medicine, and you're right -- to

your earlier point, that Google and others are doing it. But certainly those of us who have been committed to science and to research throughout our years are really looking to big data to provide unparalleled insights for scientists and researchers.

Donna Cryer:

I think one of the things that has gone unrecognized is that patients and patient leaders are part of that new STEM workforce. And one of the investments that we need to make is that recognizing that patients need to be not only invited into the process but to be educated and trained and nurtured in scientific method, in data, in health literacy, in a lot of other fields so that we can work on par with our peer stakeholders in medicine and research, and so that investment in patients as part of that STEM workforce where now we're sort of volunteers for the most part in that, but we are on the ground, and I think we're also the key to unlocking those data silos, because when you look at it from a patient perspective, looking at it in an institution agnostic or an initiative agnostic way, but really looking from what data is meaningful across my patient journey, and it might not be in a registry just on one particular disease or one particular initiative, but there may be learnings from across a microbiome, across a brain, across a liver initiative, across a kidney initiative, or infectious diseases, that we get the greatest learnings. And so I think that when looking through the eyes of patients and patient communities, you get a much more holistic, and a much more collaborative, way of sorting through these issues and identifying signals and areas for future research and also adoption of innovation, because as much as it's exciting to have the research created, I'm here today because innovation was actually adopted, and creating a national infrastructure where we can adopt innovation is as important as creating the innovations in the first place.

Nsikan Akpan: And so how do we stabilize funding for these innovations, for drug development, for education? Is it through these national initiatives? And maybe we could use the Cancer Moonshot as an example? You know there's been tons of energy behind the moonshot. There have been working groups. There's the White House Summit. But neither the House nor the Senate included funding for the Cancer Moonshot in their budget proposals, so how do we fund, I guess, these projects going forward? And this can be opened up to everybody.

Anthony Fauci:

So, you know, what you're saying is -- might even be contradictory, because when you're talking about stabilization, you mean you have a commitment that is essentially an unlimited commitment, and I think one of the things that we have to be careful about is that we forget about the stability of--this is my response to your first question is that underlying it all is the stability of the research funding in general. What Keith was mentioning. We have to pay very particular attention to that, and sometimes when we get involved with initiatives that are blips that go up that we forget about the importance of the long-term of the stability of the biomedical research enterprise. That sometimes gets lost when we're worrying about this initiative versus that initiatives. I think that I mentioned earlier, initiatives are very important because they're really catalysts for very important things, and I think getting back to your first question, that it's really very important and gratifying that this administration has been so involved in the biomedical arena for initiatives, but looking forward, when we want to look ten, 20 years from now, we can't take our eye off the importance of the stability of the biomedical research enterprise.

Nsikan Akpan:

And so does that start with Congress, or is that something that the White House could potentially --

Anthony Fauci:

Well, I think it's both. The whole funding of biomedical research historically, over decades and decades, has been a partnership of administrations and a Congress who has been very, very supportive of the biomedical research enterprise, and then something went wrong along the way on the way to the forum that that kind of broke down. And I don't think it's broke down on account of administration. I think what's happened is that we've had a difficulty with Congress, and I think that's one of the things that we have to reeducate is the pride that Congress has taken and should take in the support that they've given for the biomedical research enterprise. That's something that they should be very, very proud of, and I really would like to see -- to get back that energy that we had year -- I'm looking at John Porter who was a very important of that years ago. And I think that's something that we should try and stimulate.

John Danaher:

But I think that the stability -- Dr. Fauci, the stability you speak of, which I couldn't agree with more -- there's an onus that falls on the researchers and on the research community, and that is being able to articulate the value of the research that we do and then being able to communicate that to the American people.

Anthony Fauci:

Right. Sure.

John Danaher:

And I think that that linkage, sometimes, I think, we don't do that as researchers, as scientists, etc. We can articulate well amongst ourselves the value, but transferring that and Congress as representatives of the people, helping them to understand. And you're right. What's wonderful about initiatives is it consolidates everybody's thinking around almost a Madison Avenue type concept, but again, being able to, on an ongoing basis have that dialogue with the American people with Congress, so that they appreciate our funding priorities and the data that underpins it is the key to robust funding.

Keith Yamamoto:

Just to bring together a couple of the comments up here. I think that we want not only a dialogue with the American people where scientists and clinicians talk about what they're doing in a way that will engage the public and so they understand it and will, therefore, support it with their representatives, but also to take ownership of the process, to be involved in it. We were talking about the importance of big data. The only way we're going to really achieve big data at the scale that its needed and at the breadth that its needed is to have the public really involved and engaged, to feel that they are part of the process, that they own the process. The data is theirs. And if we can do that, then we can get the numbers. Not just numbers, but across the diversity -- addressing the disparities that are hugely problematic in our healthcare system, whether it's research or delivery and measures of social justice that really need to be addressed, and we're not addressed. And if we can get everyone involved and feel like they will gain from this process if they participate and own it, then it can make a difference in the ways that they talk to their representatives that could actually have an impact on the funding that we need.

Anthony Fauci:

Speaking of talking to our representatives--

[laughter]

I have to go join Tom Frieden in that building up there and speak to the Senate leadership just about

what we're talking about, so thank you very much.

[applause]

France Cordova:

On this point, I just think that a lot of people just don't know where their technology comes from and what went into their cell phones and their devices and their healthcare and all of that which research has delivered. Yesterday I was on a trip, and I was just in a shuttle with 10 other people -- I have no idea what they did for a living -- but we were talking, and somebody said, "What do you do?" And I said I work for the federal government, and she said, "Boy! I think the best thing the federal government has ever done was to fund the national parks," and I thought wow. I didn't say a lot. I look forward to the day when somebody says, "I think the best thing the federal government has ever done was to fund basic research." So that is the challenge that we have, and it's a great challenge, and I think just like other things that have slipped away from us, that we haven't always focused and paid attention on that grand challenge, but without it and realizing and having that internalized by everybody, we are in danger of losing our leadership position in so many areas including, you know, space and all the competition there as well on the ground in manufacturing and healthcare, so we really have a page to take out of the manual of other countries that are being ever so much more aggressive in this sense, I think, than we always are.

Albert Lauritano:

So just to actually a perfect lead-in for me -- thank you. You know I do a lot of work in Israel. Most of my time is spent on the road. It's either in Silicon Valley or in Israel, and Israel is certainly a country that has its varied politics. Probably much more diverse than even in the United States in various views, but that's the one thing they agree on. Not just how they support medical research but also technological research. In their Office of the Chief Scientist and Ministry of Economy, I mean, I have got to say, if we really want to look to a model of how to really bring academic, government, and the private sector together, you know, look no further.

They are creating hundreds of companies in a country of six million people every year. They are getting funding for these companies. They're certainly dealing with the educational needs that these people have too and the entrepreneurial spirit. They have collaboration vehicles whereas we actually get funding from the Israeli government to do collaborative research with Israeli companies and start-ups. It's a very easy process. I shouldn't say easy -- I mean you have to go to apply, but good ideas get through and get funding, and it's trounced. It goes progressive, but there's a lot that we could really learn from the Israelis, and in spite of politics, this is a system that continually pores out top people in the technology areas and top ideas that are ultimately being looked at globally.

Nsikan Akpan:

And then how do you engage the base? This will be our final question before we have the Q&A. How do you engage the base? Is it through the promotion of exciting new technologies like CRISPR? Is it through directly communicating with the public? How do you get the public and also Congress on board?

Donna Cryer:

I think you need to meet people where they are. The Global Liver Institute actually spends a lot of time in Los Angeles working with Hollywood embedding storylines about science, and I know there are other examples of that as well for where people already get their information. Rather than asking people to come to us and to learn about research, the onus is on us to show people how science and

research already affects their lives and how there really isn't--it's a false dichotomy between I'm a researcher and you're a patient. I'm both. You're both. So I think people do understand where their technology comes from and they're excited about it. How that applies or can apply to their healthcare--they haven't started seeing--there are great pockets of excellence in that, but it hasn't been spread equally, so I think meeting people where they are and bringing them examples where they're already receiving information is the first step in bringing the public to the table in this.

Albert Lauritano:

I'm a big believer in form follows finance, and a big outcome of the Affordable Care Act is to focus on, as I mentioned earlier, the change from episodic to longitudinal but also to -- on population health management. And so the key to population health management is this empowerment of patients doing more in the home, and so I think that the delivery system that we are getting and what CMS and private insurers are reimbursing, are reimbursing for keeping people out of the hospital and keeping them healthy and shifting financial dollars to more incentivized patients to be involved in this discussion. So I think as part of that, that shift, as I mentioned, I believe that shift is going to have an influence on our basic science, on our clinical research, on our health sciences research. I think that the dollars are going to follow, and as part of that, we've got to help patients and individuals understand the role that they play in optimizing and managing their chronic conditions and optimizing their health.

Nsikan Akpan:

Perfect. Great. And then I want to open up the, I guess, to the audience for questions for Q&A, and I believe they have a couple of microphones that will be passed around.

Mike Friedlander:

Hi. Mike Friedlander from Virginia Tech. I'd like to follow up on what Dr. Yamamoto said, and Dr. Fauci I know has left. This whole idea of going from basic discovery and then initiatives or moonshots, it seems to me that one of the things that may work against us is the way that we're organized, that is our institutes at NIH are organized around organ systems or diseases. Our advocacy groups are organized around particular diseases, and while these are all very effective things, in a way, you kind of wonder who's the advocate for a moonshot for, I don't know cell senescence? Or adaptive immunity? Or the life of a protein? Or any of those things that could have incredible impact on a whole host of disorders that would transcend those? How do we rally around a moonshot or an initiative around something really fundamental and get excited about it and get people to buy in?

Keith Yamamoto:

So -- hi, Mike. Nice to see you. I've been pretty tightly linked to the precision medicine initiative, and I helped to launch the report at the National Academy of Sciences that coined that phrase and enunciated what its goals were, and what that report said was that we should reorganize the way that we classify diseases shifting from organs and symptoms to mechanisms, and the reason, as Mike was referring to, is there's a crossover in mechanisms that cross disease boundaries, and so if we silo our efforts to study organs and symptoms as the way that the NIH is organized and our medical schools are organized, right? Then we're leaving information on the table that could help to move forward a whole spectrum of efforts simultaneously, so that's great. So then you ask, or any thoughtful person would say, "Well. Terrific. Then how do you organize it? Do you organize it according to biological processes and say we're going to have a National Institute of Cell Movement and Contact?"

Well, I think the scientific community would say, "Not such a bad idea." But for the people out there that we're addressing, that's not so easy to understand, so I think we need to recognize that we need to be operating at multiple levels here simultaneously and recognize that the public is concerned about

specific disease, specific ailments. They want to maintain their health, and the scientific and research community realizes that in order to do that the best and most efficiently, we need to be understanding mechanisms at the heart of them, understanding biological and disease processes at their heart, and if we can organize our effort, organizational and funding effort, that would track to those needs and be responsive to the concerns of the public, then I think that we could really move forward.

Mike Friedlander:
Sure.

France Cordova:
And as, I think the professor from Virginia Tech probably knows well, because it is the university most well-funded in Virginia by the National Science Foundation --

[laughter]

--that the NSF operates on a very different model, so we have a lot more flexibility through our calls for research institutes. Every couple of years we have engineering research centers. We have science and technology centers. We have big data hubs. All kinds of centers that are constantly forming, and then after several years, five to 10 years, they disband, and new one's form. So I think it is a very good question. I think agencies can learn from each other and how they're structured, but structure can define what you're doing. What you're missing. And we are very seriously looking at how to be even more flexible so that these great ideas and these new kinds of initiatives that you're talking about can actually get traction, and then how do you evaluate them? How do you bring together a group of merit reviewers? Where's the expertise on something that has not been well formed in the past that is a brand new area to evaluate. Where is this going to go, and how much should we fund it? It's a very interesting, creative question, and I would think that's a charge that we don't hand over to Congress, that we take on ourselves, to learn how to keep re-upping the model so that we are welcoming the best creative and most innovative ideas. And I hope that that is one of the aspirations of the National Science Foundation. Thank you for the question.

Nsikan Akpan:
The question over there? Or right there? Okay.

Male Speaker:
Yeah. Hello. I am a neurologist at Janssen. Thanks for an interesting panel. I want to come up with a question for the panel on public/private partnership. Dr. Lauritano mentioned about the unique things Israel is doing that we are very well aware of, and certainly the U.S. has some very successful public/private partnerships going, such as [unintelligible] in my field, but I wanted to know what your thoughts are on actually rather than having a public/private partnership being an outcome of question asked, install a mechanism that defectors public/private and attracts questions to it. Such like we have in Europe with IMI where you upfront allocate budgets for public/private partnerships, so I just wanted to reflect. Is that something that could be done in the U.S.?

Donna Cryer:
That's the model for my organization [laughter] -- so thank you. And I think it's certainly something that is scalable and really a way to rethink how we approach questions that cross a lot of different mechanisms or disease systems but also affect a lot of different types of people and a lot of different types of organizations.

Nsikan Akpan:
Then we have another question over there.

Aaron Mischenich:
Thank you for the panel today. I'm Aaron Miscenich [spelled phonetically] with the New Orleans BioInnovations Center, we're a business incubator in New Orleans. I've only heard one mention about small business and entrepreneurship. I was wondering if you guys have any thoughts about us outside of SBIR/STTR, that kind of thing?

France Cordova:
Well, those are very important. SBIR/STTR, and we're very proud of funding them. This morning, earlier this morning, I was at the Alexandria Chamber of Commerce -- and this was the theme of the panel discussion there, and so I'll just mention one model that we started about four years ago at NSF -- and NIH has adopted, and so has DOE now. It's called iCore, Innovation Core, and it's an instructional program that translates basic research and discovery to delivery with the product to patent a company in just a very short space of time. And we used the curriculum that Steve Blank [spelled phonetically] at Stanford developed, and now [unintelligible] in Silicon Valley, that's their model to get venture capitalists engaged and funding these great ideas, but we now have centers, nodes we call them, all over the country, that universities take their graduate students, their undergraduate students, faculty mentors, outside consultants, business people, and it's a really great combination of business schools with engineering schools too, and they look at what is the market potential for a piece of new knowledge, a piece of discovery, and does anybody want this, and what could it look like in its final form? And some ideas die. There is no market for them at least now, and other ones go on. I've seen young people give fabulous talks about taking iCore and starting companies with them. So this is something that even other countries--like the country of Mexico, Portugal, Sweden, so forth -- have adopted, and as I said, a number of the federal agencies are doing this. As I said, it's a really fast translation program, so that's one example.

Keith Yamamoto:
Yeah, I think it's sort of the best lubricant between the fundamental science and being able to take, at least, a step toward application. And I think many universities have entrepreneurship programs now. We're involved in iCore, and it's an area of great interest with our trainees.

John Danaher:
But I tell you, I like to see when there's some guts by the inventors and the people who are following it who will take it out of the university and then devote their time and actually try to build a business about it. I'm doing much less with technology transfer these days coming out of universities, because it doesn't help me address the commercial risk or the unknowns. Just in the last six months this year, from about five accelerator programs that BD works with, we've reviewed over eight hundred applications of companies that are coming into the field, coming new, that were unknown to us, and we have specific programs in place to actually take ones that we think we can help and provide mentoring. We don't invest. We don't take their rights, but we see how they can develop. And it's not just about the technology. It's how they deploy technology to patients, and then what's the business model around it. Is it sustainable?

Donna Cryer:
Absolutely. And we see that role at the Global Liver Institute as helping to define problems that matter to patients, because we find that businesses that actually solve problems are better and help them define

the market and also help promote partnerships for early partners to prove proof of concept and work with the incubators as well to help them attract support and investors. So we think that small business is an incredible tool for -- and a partner for patient advocacy organizations, and it's, you know, a point of pride that most people think that I'm based in California instead of just down the street.

Nsikan Akpan:

So that's our time. Any final comments from the panel?

France Cordova:

I'd like to take the opportunity to thank our host and PBS and just mention a little story, and this goes to Donna's comment about how each of us has a role to play especially in the public engagement with science. That I am a scientist today at the National Science Foundation, because when I was young, I saw a PBS special about neutron stars, and when I saw that and I saw how much energy was liberated by a hypothetical marshmallow dropped onto a neutron star, and I thought, "Well, how do people know that? How do they even know these stars exist?" And I decided at that moment to switch from a different major--it was English Literature --

[laughter]

-- to physics, so I have to thank PBS for its engagement in science. Excellent.

[applause]

Nsikan Akpan:

Thank you. As we like to say, we're nothing without viewers like you.

[laughter]

That applies to PBS and this panel. If you could join me in applauding our panel.

[applause]

And thank you.

Male Speaker:

Ladies and gentlemen, the forum will continue after a five-minute break. Once again, the forum will continue after a five-minute break. Thank you.

[music playing]

[inaudible commentary]

[audio break]

Michael Coburn:

If everyone could find your seats we are getting ready to start our second terrific panel of the day. Again if you could find your seats we're getting underway to stay on our schedule for the afternoon. So we are ready to assemble panel two and the moderator for our second panel is Dr. Natalie Azar who's a medical contributor for NBC news, a title she's had since 2014. Dr. Azar's primary function at

NBC is covering health related and breaking news for the Today Show and MSNBC. Dr. Azar is Assistant Clinical Professor of Medicine and Rheumatology at NYU Langone Medical Center in Manhattan. She is in private practice at the Center for Musculoskeletal Care at the Joan H. Tisch Center for Women's Health.

Our panelists this afternoon, over on our right, are Dr. Anne Schuchat who is the Principal Deputy Director for the Centers of Disease Control and Prevention, and as you heard earlier, Dr. Fauci referenced that Dr. Freiden, Tom Freiden had planned and wanted to be with us today but higher authorities called and so he's over there on the Hill. Also with us today is Dr. Steven Silberstein, Professor of Neurology and Director of the Jefferson Headache Center at the Thomas Jefferson University in Philadelphia. Dr. Andrew Bindman who's the Director of the Agency for Healthcare Research and Quality, Dr. Hortensia Amaro Associate Vice Provost for Community Research Initiatives, and Dean's Professor of Social Work and Prevention at the University of Southern California, and a member of Research!America's board. And Dr. Joe Selby, Executive Director of PCORI, The Patient-Centered Outcomes Research Institute; and again Dr. William Hait who we met earlier who is the Global Head of Janssen Research and Development. Enjoy the panel.

Natalie Azar:

Good afternoon everybody, thank you so much for joining us today. I want to say first of all that I'm very appreciative of the invitation to come here and moderate the panel today. It's certainly an honor to be in the company of these distinguished researchers, physicians, etc. And I will just say a little bit that I don't have a background in public health, although it's something that of course I find incredibly important for all of us in clinical medicine to be aware of. So, to borrow from former President Kennedy and current Vice President Joe Biden, the sort of the theme for this hour is going to be the prevention moon shot.

We would like to cover and hopefully not to -- without any redundancy, some things in the prevention public health arena such as how do we go about prevention of progression of disease, how do we stem the tide of medical errors, how do we forestall epidemics we touched on that a little bit. And also we will talk about curbing the tide of antimicrobial resistance. And probably most -- something that's a little bit of special interest to me as a rheumatologist is the idea of diagnostic accuracy in precision medicine so that we're not wasting our valuable dollars using medicines that are never going to work in a particular patient and you know how that can sort of feed into the bigger picture of prevention. So, I may open up the panel anyone can jump in I think at first, to talk about a recurrent healthcare system and our current research ecosystem. Do we place enough emphasis on prevention? Anyway Dr. Schuchat would you like to --

Anne Schuchat:

Yeah, you know it's unfortunate but prevention just is not sexy and sorry --

[Laughter]

-- but as a person who worked on immunization and vaccine preventable diseases for decades, it's extraordinary what prevention does and we really just forget about it. You know for the past 20 years of vaccinating children we've prevented 300 million illnesses, and saved 1.4 trillion dollars. But what you hear about is the concerns about the side effects of vaccines and whether we really need all those shots. So as we are clamoring for a vaccine against Zika, you know we have a lot of good vaccines we're not using enough. And I think it really takes a challenge to our imaginations to learn how to talk

about prevention, how to count up prevention, how to catalyze prevention in ways that will gain Congressional support and public support.

Natalie Azar:

Dr. Hait if you wouldn't mind giving us your opinion on whether or not we're doing enough right now. It's such a difficult and big topic, but in terms of the approach to prevention.

William Hait:

I think we're woefully short of doing enough, and one of my colleagues, a very good biostatistician, said to me when I was perseverating about this problem that we're not doing enough, he said that the problem with prevention is that nothing happens.

[Laughter]

A perfect biostatistician approach to it, but digging into that when you think about, "Well some things seem to catch on like the population takes statins to prevent the complications of atherosclerotic vascular disease, why?" Something happens -- you get to measure a decrease in your cholesterol and your doctor pats you on the back and you feel good about these things and even better it actually works. And one of the reasons that it actually works is that it gets to one of the fundamental causes of the disease. And I think one of the issues that concerns me the most in all of this is, we've spent so much time and effort in our research dollar on understanding the manifestations of the disease and how to treat it. So we're really good, for example, at lowering glucose, we've got a million ways to do it and some very, very, good drugs but we have very few ways of getting to the cause and interrupting the process that causes Type II Diabetes or even Type I Diabetes. So, I think there's tremendous opportunity because no one wants to get a disease and when everyone does they're always surprised. But we're all on our way so I think this is an area that deserves enormous input and public attention because I think the payoff is going to be massive.

Natalie Azar:

Does anybody have an opinion on gaps in our medical education and this? I'll open it up, go ahead.

Joe Selby:

Well this -- I'm not going to speak -- I'm Joe Selby, I'm not going to probably speak directly to gaps in education except I think that there needs to be some education about the point that if we could wipe out the major -- if we could address -- if we could put a dent in the major causes of morbidity and mortality that is obesity, cigarette smoking, alcohol and substance abuse trauma, we would reduce every one of the scourges of chronic diseases that we think about. So not only would we would we knock down cardiovascular disease much further than we've done to date, but we would take a good hit in cancer. I mean if you can reduce obesity, you can prevent a large number of cancers of various cancers. Alzheimer's disease is closely related to obesity and the risk factors that obesity gives rise to.

So obesity -- asthma is yet another one. I could go on and on, but that gives you the idea of the impact of the approach. Now having said that I will say -- I will echo the notion that it's not sexy, it sure doesn't fit very well into a clinical model. At PCORI we fund a number of comparative studies to try and to figure out where this kind of work is done best, but you know it has a lot to do with the society we live in and particularly the society that vulnerable populations live in. So that's a challenge I think and maybe a part of prevention is figuring out how to target these kinds of efforts to the most vulnerable populations.

Natalie Azar:
Thanks Dr. Selby, Dr. Amaro.

Hortensia Amaro:

In relation to that but also more broadly I think they're three major challenges in the U.S. today in terms of health that directly speak to the importance of prevention. One is the exponential cost rise in our expenditures in healthcare. We spend more almost two -- between two and three times more than any other peer country, about 18 percent of our GDP is devoted to healthcare costs. What's ironic is that we rate among the lowest in a host of measures of health than our peer countries, so that's number two. And number three really has to do with inequalities and disparities in health by social economic status and race and ethnicity.

So this right there should tell us that we need to take a fresh look, a more upstream look, at how we approach issues of health in this country. We're never going to resolve or increase our status -- health status through biomedical solutions these have to be public health solutions. We know that health and healthcare quality -- healthcare access and quality are absolutely important and having good care is essential. But it accounts to by different estimates ten to twenty percent of what contributes to health. So what's the 80 percent? 80 percent is really social determinants of health. And we have heard nothing yet today about that.

And so I really want to stress, I think, what is required is a total change in the conversation. We really need to bring our gaze upstream more and look at what are the causes. And you alluded to some of the conditions -- some of the conditions that effect the major causes of health like diabetes, etc, or alcohol and drug use, really have to do with social determinants of health and community conditions. Income inequality being a prime one, so I think that in terms of education of the American public -- I think the American public is not aware of our standing internationally, probably most medical students, and I haven't seen a survey yet of medical students yet, whether they're aware of this, but I think medical students really need to understand more about how the prevention of -- the promotion of health, the prevention of disease, more upstream. The clinical office is an important place, but it's not going to do it alone.

Natalie Azar:

You know, just anecdotally, I've been in practice for 15 years and the focus has shifted dramatically inside my exam room from you know where it is today where it was 14 or 15 years ago. When I was training as a rheumatologist, nobody taught us about obesity and how it affected [unintelligible], nobody taught us about nutrition, and nobody taught us about an anti-inflammatory diet, these were all things that were taught to me by the patients. So in some capacity I feel like you know with more media and you know news reporting and health reporting, there is a message out there.

Nobody wants to hear anymore that they're supposed to exercise and eat a Mediterranean diet, I think everybody knows that. But it's actually implementing those things. And what you're talking about really spoke to me especially about the disparities that we see in our country that, in more perhaps urban areas, with people of means you know generally I think the consensus would be that -- the people are healthier, right? So any other -- I'd like -- I'm sorry Dr. Bindman, -- I'm sorry, Bineman or Bindman?

Andrew Bindman:
Dr. Bindman.

Natalie Azar:

Dr. Bindman, yes, I would love to hear your impression so far of what we've talked about in particular the disparities which I think are very salient.

Andrew Bindman:

Well, I think you put your finger on an important issue. I mean one of the things that is critical is to think about how we move new treatments whether they be about prevention or in other areas out to the front lines of care. And I think if we are not systematic about it that we allow our knowledge to in fact be disseminated in a way that is -- does lead to differential uptake of it because people with greater means are more likely to have access to providers or the resources where they are going to be able to take advantage of that kind of opportunities.

You know in the case of prevention, on the one hand, you identify some aspects of it that are well known but there is often a need for synthesizing knowledge about what our best strategies are around prevention and making sure that knowledge is moved in a systematic way to the front lines of care. And if we don't do that, that is where we'll get some of the disparities start to occur between those who have means and those who do not in terms of what the available resources are to be able to attack the issue.

I think we also have a problem in many cases of figuring out what are the best ways to organize our resources to address these prevention needs in the healthcare setting. Right, so, in the case of trying to lower cardiovascular morbidity and mortality, most physicians -- most primary care physicians would know, for example, what risk factors they're supposed to attack. But do they have in fact the capacity within their offices to think systematically about saying, "Which of my patients do have their blood pressure out of control -- which ones of theirs do not have their lipids under control." So how do we systematically build teams and care and organized care in a way that we're taking on prevention in a population type approach?

And I think we have made some progress on these things but I think we have to invest in the capacity in the systems to allow this to happen. I think we are seeing things happen in healthcare in terms of systems forming, physicians are consolidating, in many cases into larger organizations, but we have to better understand what they're capacities are to really do population management and to make prevention an important part of what helps them to control costs, and improve the quality of care for their populations.

Natalie Azar:

Very good, thank you I could go on and on about that one in particular. I'm going to switch gears a little bit -- Dr. Silberstein, pain specialist, migraine specialist, can we talk a little bit about the other scourge in our society now which is the opioid epidemic and how we approach -- and wonderful and I applaud you know new recommendations for opioid prescribing for primary care physicians who do not see pain every day. But, rather I should say, probably do see pain every day, but haven't been trained in pain management do we have another tool, a more effective way to communicate, or a more effective message rather than throw your Oxycodone out in kitty litter and then leave the patient still in pain. Because that's what people are -- I think that's what the public hears when we say get rid of your narcotics.

Steven Silberstein:

We've gone from one extreme to another. I think the opioid epidemic is a mal-event related to making pain the next vital sign. Everybody was being judged on asking people about their pain and treating it

with a painkiller. Think about that. Instead of saying why do you have pain and what can we do to get rid of your pain they gave a Band-Aid. Now we're in the situation -- now you have pain, we'll just not give you anything to treat your pain. The message is wrong.

If people have pain, we need to know why they have pain and what can be done about it. Back pain, probably the best treatment is physical therapy and nonsteroidals, headache, my specialty; there are 36 million Americans with migraine. According to the World Health Organization, it's as disabling as somebody who is quadriplegic or acutely psychotic during a break and it's one of the major causes of disability in the United States. Migraine is interesting; somebody will one a year, somebody will have one a day. One of the biggest problems we have is that people who have infrequent migraine and take either butalbital or opioid-containing compounds convert from episodic to a chronic migraine and have migraines every day of their life.

So going back migraine, if you have frequent bad headaches, first and foremost what's the appropriate, correct, treatment that will not aggravate the situation and prevention is the way to go. What do I mean by prevention? There are 36 million Americans with migraine. Proper diet, exercise, yoga; they will prevent episodic, recurring, chronic migraine. If the headaches become more frequent, appropriate preventive medicine will work. There are 2 million Americans, two percent of the population of the United States, has headaches every day and the majority of them are over using a painkiller, a Triptan or a Butalbital. We should get away from the pejorative in saying, don't treat your pain, we should say treat your pain appropriately and help these patients.

Natalie Azar:

Thank you, Dr. Schuchat this is for you. We're going back to Zika and back to Ebola. I remember -- I was asked a question why -- well how did we get here you know Ebola has been here before and we're getting that question a lot. How can we find ourselves in a situation with no vaccine and no treatment? Do we have to accept emerging epidemics as the new norm? Right with travel, and industry, and technology, and the movement of people all around the world is it just a matter of time before the next epidemic sprouts up? And we're -- are we always playing catch-up?

Anne Schuchat:

You know I was thinking about your remarks at the beginning of this session that you know in 20 years we're going to be as healthy as our cars are. But the mosquitos and the bacteria are not going to be there and they're not going to be following that playbook of you known under control and anticipating change. We know that microbes are changing constantly and it's not really a question of if there are going to be other really difficult problems, but when.

We're really struggling at the CDC, at NIH and other places because we're not having any separation in time from one emergency to another. You know, in January of 2016 there was a new case of Ebola in Sierra Leone, you know, three months after they'd declared things all finished. And that was the same month when Microcephaly was linked to the Zika outbreak in Brazil. Our Emergency Operation Center has been activated continuously since Dr. Freiden got there.

Cause and effect I don't know --

[Laughter]

-- but just saying. But in any case, we are -- really you know the other thing I was thinking of was the comments earlier about the start-up. And I'm thinking in Atlanta if you come to visit the CDC we have

our own little start-up company called the Zika Response Team, and they are really working twenty-four-seven dealing with this, it's the most complicated emergency we've ever had. We activate all the time, we have infectious disease problems all the time, but we've never had our Birth Defects Center activated and co-leading the response. You know, we have mosquito control experts at CDC, but we don't have very many and the country doesn't have very many anymore either. So in terms of education gaps, you know, go out and get some more entomologists those of you who are at universities.

[Laughter]

Because we really need them. You know Zika is so complicated because it's pregnancy, it's mosquitos, it's poverty, it's this fabric of the country that's lost its infrastructure for mosquito control and for surveillance. You know, the communication issues are massive, the environmental questions people have about the pesticides, so we're really working non-stop and that is why Dr. Freiden and Dr. Fauci are elsewhere right now trying to make sure that we have the resources to continue.

But I really don't think it's a question of reaching a point when things will go back to normal we really need to just get better at dealing with these and be able to deal with the major priorities in health in general as well as the emergency response. And so for a number of the politicians they are seeing that this idea of a public health and emergency response fund might at least help take some of the politics out of at least getting started on a response.

Natalie Azar:

Okay, thank you, Dr. Schuchat. I would like to open this up to anyone who would like to comment on it, antibiotic resistance. We hear about this quite frequently and I don't know if you all received this e-mail today, but I did, about the Federal Prize Competition. An innovative --we're charging researchers, biotechnology firms, etc, for innovative ideas to combat the emerging problem of antibiotic resistance it's called The Antimicrobial Resistance Diagnostic Challenge. 20 million dollars will be awarded to the winner to come up with novel ways to you know in the office setting determine immediately if a bug is going to be sensitive to some things so that the wrong antibiotic isn't prescribed and probably more importantly for the majority of Americans to distinguish between viral and bacterial infections in the office so that we you know -- obviously we know that completely augments the problem. So, does anyone have a comment on that?

Andrew Bindman:

Well just to tie it just a little bit to your comments about prevention earlier in this conversation, I mean, I think one of the best ways to reduce the use of the wrong antibiotic is not to need it in the first place. So a big part of this work really involves making sure that we are employing the best practices regarding, you know, particularly in hospital and other institutional settings that we are not spreading infections through our care. And so that we are practicing in a safe way, and I think that's something where we need to bring additional attention.

You know, we have had success in this country and in identifying practices that can lead to reduction of infections associated with central lines and with the use of urinary catheters, that have dramatically reduced infections in the ICU and in the hospital setting. We need to bring some of that same kind of mentality to the nursing home setting and to other practice locations. Because part of this is not just choosing the right antibiotic but not needing the antibiotic in the first place. So that's a big part of what we need to do. And we need to create accountability, stewardship around the use of antibiotics in general in which there is the right kind of choices being made. But I do think prevention has an enormous role to play in helping to contribute to antibiotic resistance.

Natalie Azar:
Dr. Selby.

Joe Selby:

Just a small add on there, we've seen -- I think this may well be an instance where performance feedback -- more in the way of performance feedback would help clinicians see how their practice in using antibiotics compared to their colleagues. We've seen it work in a lot of other areas; physicians actually eventually get very competitive about doing the right thing when their fed back data. And I don't think they've gotten a lot of that yet, the emergence of big data, the emergence of electronic health record-based data networks, could really help link up and create good performance measures that could then be shared.

Anne Schuchat:

I was just going to say I think that that's absolutely right but we think there's sort of three prongs here that you need the clinician to be considering prescribing in a different way. Feedback can help but one thing we found is that clinicians need to know your doing something about the public or the consumers and they really like knowing that we're also trying to address the social norm or the parent that's asking for the antibiotic, or that public demand, because physicians sometimes say, well I wasn't really going to give it but they really wanted it. So I think feedback can be twofold.

And then the third part of this is really that system approach that it's not enough for one institution to get their act together, or one outpatient facility, but with the really scary bugs, we're seeing them you know crossed through the system. So you need a coordinated care system to be working together.

Joe Selby:

I would make the same comment of the over use of neuroimaging if the patient demand and the doctors fear that if they don't do a study something will be found and they'll be guilty of malpractice. So I think that's a real issue. Patient's want something it's easier to say yes than to say no. And I think we need to address that issue in terms of all prevention. Too many false negatives.

William Hait:

I do think that the challenge is right on because one of the key elements is making the proper diagnosis rapidly. So if you have a busy practice a patient comes in with a kid, a cough, whatever, if it's going to take three or four days to know whether it's influenza, pneumococcal pneumonia, whatever it is that's put's a -- that doesn't function. But the development of powerful point of care diagnostics so at the end of the visit, you might be able to go back to the patient and say it's not a bacterial infection it is this particular issue and here's what we prescribe for this. And that I think would be number one very helpful and number two would tamp down the argument but I want an antibiotic anyway. Now there's some ammunition that the physician says, no that the patient doesn't really need an antibiotic. So I think he's right on.

Anne Schuchat:

Just one more comment. I think there's sort of a connection between this discussion and the earlier one though because some of the really blockbuster research innovations can facilitate improvement here. You know we worked in the '90's on trying to improve appropriate antibiotic prescribing among pediatricians and talked about you know most ear infections don't need antibiotics trying to push watchful waiting. Well, once the pneumococcal conjugate vaccine was developed, introduced, widely used, the scary problems of ear infections in children really diminished. And it was much easier for

clinicians to be willing to adopt watchful waiting. We saw a great reduction in antibiotic use in pediatrics because sort of those bad things was taken out of the equation. And I do think both clinicians and the public you know once they know they're interventions for the things you're worried about, are much more amenable to more conservative approaches.

Natalie Azar:

Thank you, Dr. Schuchat. So this might be directed to Dr. Bindman but anybody can jump in. Medical errors third leading cause of --

[Laughter]

Andrew Bindman:

I didn't know that was the whole statement or not. I didn't know if you wanted me to write a book about it or so --

[Laughter]

Andrew Bindman:

So medical errors are absolutely still, unfortunately, a major problem in the healthcare delivery system. It has been identified through epidemiological studies that it may well be the third leading cause of mortality in the United States certainly a very significant contributor as well as to morbidity. And you know I think as a practicing physician this is extremely disheartening. No doctor wakes up in the morning thinking gee I hope I don't kill anyone today I mean of course you think that a little bit in the back of your mind, you're really thinking I hope I can cure someone today. And so it is you know not the goal of any physician to give harm, in fact, that's part of our credo is to you know do no harm to patients. And yet you know it's a very challenging and vexing issue. We have had real success in some aspects again have seen reductions to some extent in hospital-based mortality through some of the activities that have been taken to reduce hospital required infections and complications. But we still need to make more progress on this.

So I mean the investment in this issue is just a rounding error compared to the investments that are made in the leading causes of death, cancer and cardiovascular disease. And if we want to take seriously the morbidity and mortality associated with patient safety issues we're going to have to dramatically increase the investment we make in this area. And I think it's the evidence is there that we know how to find things that we can attack and to give tools to health systems to make a difference and to start to have an impact. But we're not doing it enough in enough areas and on a broad enough way. So it needs to be taken on.

One area that you touched on that I think is a very significant area where we can really start to make a difference is in diagnostic error. Because if we don't get the diagnosis right in the first place, then all the things that we do to the patient afterwards are things that can just cause problems for them. Just lead to side effects or complications and so forth. And so I do think there's tremendous opportunities to think about what are the ways that we can improve -- that the diagnostic process itself, how can we bring more intelligence at a time that often a lot of decisions are being made very quickly in emergency departments or in acute -- or other kinds of acute settings and to make that decision making more intelligent with the help of information systems, with the development of better communication between the lead physician involved in making the diagnosis, working with consultants, with the laboratory, with the imaging department. How do we make sure information is not lost and that information is being synthesized in ways that really is leading to the right diagnosis.

We estimate there could be as many as 12 million diagnostic errors per year in the United States. So this is an area where's there tremendous opportunity with research to start to really make a difference in reducing the amount of harm that comes from making the wrong diagnosis and going down the wrong path.

Natalie Azar:

What I'm hearing is that we need a moon shot for everything.

[Laughter]

Right, I mean if we had, one second Dr. Silberstein, if we had the capacity to have all the hospitals in the country and all the electronic medical records and all of everything, be able to communicate this is what's working for us this is you know that kind of thing. Rather than little pockets, little pockets are doing it well, little pockets are doing it poorly. Because what I hear -- you know when we learn about the cancer moon shot it all makes perfect sense. Share your data, share your patient data, share your you know share the genomics, share your outcomes. It's just a thought I had. Dr. Schuchat.

Anne Schuchat:

Sure well, I think we need learning systems. And so we need you know the clinician to be getting data back that can improve their care, we need team-based care that means different people are checking in on different parts, and we obviously need to be measuring and learning from what we're measuring, and committed to continual improvement. So I think you know the thing about the idea of a moon shot is you have a really clear goal. You have a really -- steps that have to be carried out. Everybody is moving along the same direction and you're measuring how you're doing. In healthcare and in prevention we need to measure. You know it's just not something that people get excited about but it's really, really, important.

The issue of diagnostics though we have to be really careful because the incentives for diagnostic testing are not there. I mean you just take something like Zika and how much difference it would have if we had a good test for Zika a while ago. I mean, how many women would be relieved because they wouldn't have to worry about that next pregnancy. And the scientists tell us it's just really hard to get there. Are we investing in that kind of test, well what if we only need that test for a few years you know. So we just you know when we think about a medicine that you're going to take every day forever you know a disease that 20 percent of the population has there's a lot of incentives for people to work on that. But for diagnostic -- you know very specific diagnostic tests we haven't quite got there. And you know a 20-million-dollar prize is a good thing but it's not necessarily enough for a whole system approach.

Natalie Azar:

Dr. Amaro and Dr. Silberstein I know you each had a comment, sorry. Go ahead.

Hortensia Amaro:

So on the question of the moon shot, I think we you know and also focusing on the issue of prevention we need a moon shot on prevention. But still, you know the conversation I notice is focusing very clinically still. So we only have considered a very small part of the prevention spectrum. So if you think of everything you know moving from downstream to upstream, from you know the doctor's office and what can be done in contact with the medical care system we've heard a number of those

issues pointed out. Then you need to go before or outside of the Doctor's office what is relevant and important.

So there are things individuals can do related to prevention and you know we've had some efforts in terms of health promotion at the individual level, you know the whole lifestyle kind of approach of what people should do should not do. But there we know that communities are really relevant to what in fact people can and can't do. What they can afford to do. Maybe the provider says, you know, eat a healthy diet, you know get connected to a nutritionist, but the person really lives in an area with a food desert, you know highly segregated, very poor, can't afford to go to the fancy food store or get the healthy food. So what does that mean for prevention. And then you know if you move further upstream and look at what are the policies that we have in place regarding -- we know that some of the social determinates have to do with income, poverty, income inequality, so we know that these community's also have generally worse transportation systems, which means you don't have access to jobs. Income and education are the most powerful predictors of health status.

So how we cannot just afford to focus on what happens in the intersection with the medical system we really have to face up to the fact that we have more children living in poverty in this country than our peer nations, that children below age five have a higher chance to die in the U.S. than in our peer nations, and what does that mean for prevention? So we really have to dedicate you know a significant amount of effort at identifying how we're going to move upstream. And there are -- there is a movement in the country doing that in public health, the Robert Wood Johnson has the Cultures of Health Program as do a number of other foundations that are moving upstream. A number of anchor institutions, hospitals, and universities, under the National Task Force under the Anchor Institutions and the Democracy Collaborative have developed not only approaches but metrics for how anchor institutions can help improve community wealth and conditions that affect health based on the social determinants of health. That is where we need to be moving.

Andrew Bindman:

You know I think one intermediary step that could move us in that direction is an investment in health systems. We're seeing a real movement toward health systems taking on responsibility for populations. Our payment models are moving us in that direction and I think if we better understood how health systems can play a contributing role to implementing prevention strategies, the roles that they can play through using their information systems to help us more quickly learn about what kinds of practices actually make a difference and improve patients' health and can also be part of using that information system to support decision making to improve reduction of diagnostic errors and so forth.

So I think a lot of investment in health systems as practices are consolidating into them, provides a means to get to some of these population factors as they take on some of that responsibility. And give us an opportunity to understand how key organizational factors can really contribute toward health, toward reducing you know safety errors, and toward helping us to gather data more quickly about what practices are going to lead to the most -- the highest value in terms of improving patient's lives.

Natalie Azar:

Thank you Dr. Bindman we have three comments quickly and then we have to open up for questions. Dr. Silberstein, Dr. Hait, and then Dr. Selby.

Steven Silberstein:

I think it's extremely important getting back to the concept of errors. There are lots of different errors. Error one: I may have seen a patient who has seen five other doctors and he was never

diagnosed not because the other doctors knew less than I did, but with an extremely rare disorder. And we see this all the time. Error number two: Failure to ascertain a part of the history that's relevant to treatment. Best example: you give a patient medication they've had a reaction to a similar drug and they get a severe drug reaction. Three: ordering imaging tests. You get an imaging test you don't get the result or you don't get the lab test and things get worse.

So I think when you're talking about errors you need -- before you look at systems you need to look at the nature of the error that can be corrected by a system. Something very simple. You order a study on a patient you make sure the patient gets the copy of the error -- of the lab test or the imaging and you instruct him to call as soon as they get it. That means one: they've got it. Two: you know when he gets it because often enough I won't get the lab tests for a while. Three: errors in the hospital. Failure to operate on the appropriate side. I think that's been fixed. You talked about infections in the hospital that's getting better. So I agree the systemic approaches will help it but they will be different for the type of error. And for example, a complicated case the diagnostic error, no system will fix that.

Natalie Azar:
Dr. Hait. Thank you, Dr. Silberstein.

William Hait:
So I think there might be a piece of this that is going to sound the sexy part of prevention so I'll give it a try. So here was the question that we asked we're taking on this world without disease, we're starting with lung cancer, so we want to eliminate lung cancer by preventing, intercepting, and curing it. So the question we would ask is what causes lung cancer. The immediate reaction, well, people will say well cigarette smoking, of course, is a cause of lung cancer. But then if you say what causes cigarette smoking there's a kind of a silence that goes across the room and then people come up with some things that are very soft, well, stress maybe, or peer pressure, but if you then dig into it well what is this science underlying someone under stress that causes them to do something that's so harmful to themselves. And this area which people have termed behavioral science I was thinking maybe we need a new term for it to really dig in and get an even deeper knowledge than we currently have. So I thought of psychobiology but then I thought maybe it should be psycho molecular biology, and then I thought it should be psycho molecular and cellular biology, but as an oncologist, I thought it should be psycho molecular immunobiology or something like that.

[Laughter]

But I do think that the knowledge that is going to emerge much more detailed -- at a much more granular level of why we choose certain behaviors. And when that knowledge begins to emerge then you'll be able to get to solutions that are actually addressing the causes that underlay all of the subjective things that we talk about when we talk about people's behaviors.

Natalie Azar:
Thank you, Dr. Hait. Dr. Amaro after Dr. Selby. Did you forget what you were going to say?

Joe Selby:
No, no.

Natalie Azar:
Okay.

[Laughter]

Joe Selby:

Heck no in fact I was going to reinforce what Dr. Amaro had said because I'm just so convinced I think back to the chronic care model -- Ed Wagner's chronic care model and even that model from 15 years ago showed this intersection between the health system and its information systems and the community and other agents in the community. I just came back from the Zuni Indian Reservation or Pueblo in New Mexico and it's a community of 6,000 people, few -- not many people work because there just isn't any work they're isolated. Obesity, mental health conditions, substance abuse, and alcohol are just completely rampant. I think the role of a lack of hope has a lot to with why we take up smoking and are resistant to quitting or why alcohol and substance abuse play in it. And why a -- there's a disinclination toward prevention or maintenance of health. And I don't think a healthcare system is -- I mean they had an Indian Health Service Hospital absolutely smack dab in the middle of the Pueblo and people didn't use it trust it.

So I would add to the various scientists that you listed Dr. Hait, a sociologist. And I think that educators -- certainly that has to be part of the solution and if I could add one more very perverse little comment. We did -- about preventing medical errors one of the best ways probably to prevent hospital-based medical errors is to prevent hospitalizations.

[Laughter]

And a good way -- one way to prevent hospitalizations is to prevent inappropriate emergency department use. Because if you visit an emergency department all other things being equal rather than a primary care setting your more likely to get hospitalized and then experience these. So primary care I think and the use of primary care and I know there's a resistance to using primary care in some communities but that can --

Natalie Azar:

I loved that last comment and I have to end here Dr. Amaro to open it up for questions but hopefully one of the questions will address your answer that you have at hand. So we only have a few minutes. Go ahead.

Joe Selby:

Well I'd love to hear --

[Laughter]

-- more from Dr. Amaro so I'll ask a question in that area which is a lot of the comments have been about social community determinantsof health your opening comments and -- but you also said in your opening comments that physicians need to understand that better. And my perception has been that there's -- although we've talked about convergence and getting together a lot in the first part that there's been a historical siloing between medical care, I was trained in medicine and learned very little about population health and community health. And between public health or community and population health. And in fact, often the communities disparage each other frankly on certain health issues. I know many of you though live in both of those worlds and I wonder is that part of the problem is there a way -- I mean it would seem to me that physicians could be a great and powerful tool with promoting community health. How do we get there from here?

Hortensia Amaro:

Okay, so I will try and get my answer in and answer your question.

[Laughter]

So you know I think there is a story that we have believed in this country about health and individual choice. And so you know kind of targeting or answering your question the question is also about marketing to certain populations from the tobacco industry. The answer is also about inequities in exposure to toxic chemicals in minority communities and in poor communities. I mean so you cannot just attribute this to individual choice. A lot of the contextual factors shape norms and shape the possibilities of what your choices are. So we have to really think again more upstream and in a more complex way.

Absolutely healthcare professionals including doctors, nurses, and other healthcare professionals have to be part of this. So if we're thinking about the spectrum of prevention that I mentioned we focus on you know what we've discussed mostly here which is sort of at the point of clinical care what can be done to improve health. But we move upstream and doctors have to be tied into that, nurses, but also other health professionals, and other stakeholders. So cross sector collaboration with transportation, with economic development, with housing. These are all issues that impact health and that shape opportunities you know with education okay? So we have to include in the conversation earlier this morning we talked about broadening the conversation and bringing other people in. You know not only patients but community stakeholders. So we have to make – I think the conversation has to change to understanding that to make the health of individuals in this country better we have to improve the health conditions in communities and the opportunities to be healthy. And that includes access to care but it also includes opportunities for employment, for housing that isn't dilapidated, you know for access to transportation that gets you to the food store that has healthy foods, or to employment. These are -- you know people sometimes tend to think this is too big for us to think about but the evidence over the last 20 plus years in public health is there that these are the determinants of health and if we really want to make a difference and we want to improve people's health we cannot wait until or only intervene at their point of interaction with a medical provider. We have to really learn more and talk bring into the conversation those other stakeholders from across different sectors, the business community, etc.

So I think that the education of healthcare professionals, as well as individuals in these other sectors, would benefit from opportunities to come together and take on some of these challenges with solutions that come from different disciplinary approaches. And that's happening in some venues so you know I do have hope. But I think we have to change our conversation from talking about healthcare and very downstream biomedical solutions to moving upstream to what really are the major determinants of health. And income inequality is a huge one in our country. We have increasing income inequality more than our peer nations, major determinants of health.

Natalie Azar:

Dr. Bindman and Dr. Selby.

Andrew Bindman:

Just real quickly, I mean I couldn't agree more with those comments but I think the key to bringing the healthcare community into this is a change in the payment modeling. And clearly, there's a lot of

experimentation going on with that. I think we need to continue we need to accelerate that; we need to figure out how to make healthcare professionals responsible and rewarded for keeping populations healthy. I think that the payment incentive is a good part of it but it is not sufficient. We also need to give tools to health systems to study what are the best ways to actually practice population management. We can't just assume that this is known by health systems. Because they haven't been practicing it before why should they suddenly know how to do that now.

And I think we need to invest in understanding what it is -- and researching the practices that make a difference on a population level and so that our payment incentives aren't just the carrot hanging out there that are frustrating healthcare providers, but are in fact helping to incentivize them and give them the tools in that directions to actually do these things that reinforce and bring about prevention and make populations healthier.

Natalie Azar:
Dr. Selby.

Joe Selby:
I can't agree more that bearing risk for a full population is going to make you think very quickly about the full community. One other point about the what can physicians and other clinicians do. I think there's a lot of evidence that when you do draw trainees for clinical professions from communities, they disproportionately go back to those communities. And so I really want to give a shout out to the programs that are emerging in a lot of places now -- new medical schools, new nursing schools, and other professions pharmacy, physical therapy, of really reaching out to these communities even if you have to start in grade school getting people on tracks I think that helps -- it could go a long way toward keeping healthcare really culturally sensitive and geographically located right in the communities.

Natalie Azar:
Excellent point. Can we take another question? Yes?

Male Speaker:
I just want to start by giving Dr. Hait an answer perhaps for that term -- I'll just call it neuroscience --

[Laughter]

-- and of course, there is an entire sub discipline of neuroscience that deals with decision making. And very much at the individual level with respect to addiction and substance abuse and at the group decision-making level, and at the level of policy. So in all seriousness, there is an emerging field and I think for Dr. Amaro, they're not as far apart as they may seem. So the issues that you're talking about I think are critical but there are connectors to the biomedical sciences to understand better the social science aspect of the higher level population health decision making and I think really us realizing that and getting those communities to talk to each other will inform it through science from multiple levels.

Hortensia Amaro:
I would love to do imaging of some of our elected officials.

[Laughter]

Natalie Azar:
Okay, there you go. Okay do we have another question?

William Hait:

Just a comment, I think it would be you know fantastic if in medical schools today the neuroscientists were teaching side by side with the social scientists. That would be one interesting curriculum, I would think.

Natalie Azar:

[affirmative] Okay if there are no more questions then that will be it thank you.

[Applause]

Male Speaker:

Ladies and Gentlemen the forum will continue after a short break. Once again, the forum will continue after a short break. Thank you.

[audio break]

[music playing]

Male Speaker:

Ladies and gentleman, please take your seats. The forum is about to begin shortly. Once again, please take your seats. The program is about to begin. Thank you.

[crosstalk]

Male Speaker:

Ladies and gentleman, please take your seats. The program is about to begin. Please take your seats.

[crosstalk]

[music playing]

Michael Coburn:

If you could find your seats, that would be terrific. They're getting ready to start our third and final panel of the afternoon.

[crosstalk]

Okay, this afternoon for our third and final panel, we are joined by Geneva Overholser, who is our moderator for this panel. Geneva is a senior fellow and consultant at the Democracy Fund. She was editor of the "Des Moines Register," which led the paper to a Pulitzer Prize for public service while she was there, and has been an ombudsman of the "Washington Post," a member of the editorial board of the "New York Times," and syndicated columnist for the "New York Post" writers' group. She serves on the boards of the American -- Academy of American Poets, the Rita Allen Foundation, Northwestern University in Catarrh, and the CUNY Graduate School of Journalism.

And our panelists this afternoon over to the right, we are joined by the honorable Kweisi Mfume, a former member of Congress and also board member of Research!America. We have us Dr. Jean-Christophe Tellier, CEO and chairman of the executive committee of UCB; Dr. Robert Califf, commissioner of the Food and Drug Administration; Dr. Emil Kakkis, president and founder of the

nonprofit EveryLife Foundation for Rare Disease; and Sudip Parikh, the senior vice president and managing director for DIA Global and a member of Research!America's board of directors. Thank you.

Geneva Overholser:

Thank you, and welcome to the final panel of the afternoon. I am delighted and honored to be here. I met Mary Woolley at an event in Cambridge a few weeks ago at a convening sponsored by the Academy of American Arts and Sciences, a project that I am co-chairing, called "The Public Face of Science," that fundamentally is trying to figure out how the public relates to science and how we might affect that for the better. So, I've learned a great deal, and I'm grateful to be here. I must say, I miss having Mary here, but as a grandmother I thrill to the choice that she made.

So, we have a terrific panel. We're going to be concentrating on the Food and Drug Administration largely, which has so much to do --

[laughter]

Robert Califf:

Is this called like a bull's eye right here?

[laughter]

Geneva Overholser:

You're seated in the middle for a good reason, right?

[laughter]

Geneva Overholser:

It has so much to do, as all of us know, with many of the things we've talked about already, and it's facing its own challenges and opportunities and much under discussion in that splendid dome or under it, but I would like to begin sort of to set a baseline without putting too much of a spotlight on Dr. Califf.

You have been clear about your priorities, and I'm eager to hear you just sort of brief us on what you have set forth as your priorities and kind of the status of them, if you would.

Robert Califf:

Sure, so, I mean, I think as people in the room probably know, I am a latecomer to a point -- a presidential appointment requiring confirmation, which is quite a lengthy and interesting thing to go through, but having gotten through it and having been at the FDA for about a year before starting as commissioner, I had a chance to see what was going on, and far and away given the amazing opportunities and challenges of the upcoming science, the number one issue for me has been the workforce at the FDA.

And we'll get a chance to talk more about it, but why don't we just use the term "gene editing." I'll just let it stop there. We'll get back to it later, but if you think that you can regulate gene editing without an amazing scientific organization, you're out of your mind, and so -- and yet we're in a federal system, which is devised across the board for the entire federal workforce to be fair to

everybody, and we've got a lot of special needs, and so that's been a tremendous effort, and we are making progress. I, you know, I won't go into details in the interests of time.

Issue number two for me is what I call evidence generation, and I think the easy way to think about this is we have to make decisions every day. You know, the great thing about academia that I came from is you did a study, and then you'd write a paper saying more research is needed.

[laughter]

At the FDA, you do your research, and then you have to make a decision, and a lot of people's wellbeing depends on a good decision, including a major part of the economy -- about 20 to 25 percent of the whole economy. But I noticed right away that when we have really good evidence, there tend to still be arguments because there are winners and losers when you make competitive decisions or even decisions, you know, that are not competitive on the face but change -- you know, most of what we do changes market places.

So, there's still heated discussions, but they're relatively civil and well-informed. Then, we have to make a number of decisions where we frankly just have bad data. We don't have good information, and those tend to be dominated by opinion, politics. No one is satisfied, but there are winners and losers created, and internally at the FDA, it doesn't feel right because you have less confidence in the decision that you're making, but, you know, there are decisions that we have to make in that regard.

So, as a contrary, and it relates to, you know, the part I heard of the last two discussions -- you know, if you ask me what should link health care and public health, you know, in the past it was hard to link because we had human communication as the issue. We now have electronic records that pertain to the whole gamut. They're there, they're available, but we haven't made them into the information sources that we needed

So, tremendous effort, both at the FDA and across the federal government to take advantage of the resources that are developing in the way of electronic health records, claims data, geospatial information systems, you know, and linking these things together so that we can back up many of the assertions that were made, I think, correctly and devise strategies and implement them and measure how we're doing and then refine.

So, evidence generation is number two. I'll close by just saying one of the great things that happens at the FDA when you get nominated by the president -- first of all, you thank the president -- "Offer me a job in the Oval Office" --

[laughter]

"I've got it made" -- as you walk out., and then you realize you actually don't have a job because you can't get the job unless the Senate confirms you. And so the whole FDA goes to work and asks the question, "What can we teach this idiot that would allow him to get through a Senate confirmation hearing?" And it's an amazing compilation. I got 150 issues. The whole FDA comes together and puts together briefing documents on these really complex, difficult issues that are just amazing to learn about, and out of those 150, we selected 16 with the time that we had to focus on, and, you know, some of them are -- have already been mentioned -- emerging threats to public health, like infections and terrorism. The opioid epidemic is another. Precision medicine is another.

I could go down the whole list, but I won't, and I'm pleased to say we're making, you know, I think, pretty good progress on all, but I will -- I do want to emphasize what I think the last two panels have said. If we don't have an emergency defense fund to support what I think is a -- I didn't know much about it, but the effort across federal agencies when there's a public health emergency is profound and amazing to see, but if it's not funded, you're essentially going to take away from all the things that everybody else is counting on for their routine, day-to-day activity, and so we've got a real problem there that needs to be dealt there. So --

Geneva Overholser:
Right.

Robert Califf:
-- it's out there.

Geneva Overholser:
Thank you. At the risk of making you feel even more like more teaching for the idiot, which is not the intention, I wonder if we could go down and just each of you, starting with Dr. Parikh, give us a sense of what would you emphasize on his agenda, what would put on it that's not on there, what would hope wouldn't be on there, or any other response you'd like to make.

Sudip Parikh:
You know, I'm happy to do that, but I think he's heard from about a thousand different people about what should be done. I would take a step back and say I'm -- this is not your father's FDA. You know, if -- I've been associated with this process for 20 years now, and when I first got to D.C., FDA was insular, it had no science to speak of. It was not loved by anyone. In 2005, there were worries about not even having enough dollars to pay the workforce they had.

That is -- that is not the case. This is an FDA that reaches out. It's proactive. It has -- you know, Dr. Califf and his team are out at every conference I can think of, and they're proactively engaging with industry in ways that they never did before. So, we've come a long, long way -- a very long way, and so I think it's important to recognize that.

If I -- if I think of it in terms of what would I suggest, number one, the workforce -- I agree completely. The second is continuing to maintain this outward face. That building over there -- the Capitol -- is incredibly important to the FDA. You know, I'm -- I think of the funding mechanisms for FDA. PDUFA is a wonderful thing. It's an amazing -- it's amazing we even came up with it. You know, it's amazing to me that we were able to come together -- both parties -- and come up with a way to fund the FDA that was outside the appropriations process. All that conversation we've had in the last two panels has been about how do you fund these things in different and extraordinary ways. PDUFA is a primary example of a success story, so I want to continue to have that external face towards Congress.

Geneva Overholser:
Thank you. Dr. Kakkis.

Emil Kakkis:
Well, I -- we work on accelerating biotechnology innovation for rare disease, and really for the rare disease world, we're in a real golden age of new drugs being developed, and there's so many new technologies, new strategies, or coming forth with solutions to disease we didn't think could be solved,

and that's creating, I think, an enormous strain for the FDA because there's so many diseases that they may have never seen before -- first treatment ever being developed. The technology is novel and not well understood, and I think that's putting a particular strain on the agency and the current structure of it, and I think one of the things that -- and we've talked before -- that I think that increasing specialization of the review divisions and the people that have to do this that they have -- and they have to have enough time to do the scientific background, go to the conference, be connected, and we think that something has to happen in order to allow the FDA to keep up with this burgeoning number of rare disease treatments that are coming forth.

We have the opportunity to really change care for these patients, and I think it's important for the FDA to have the resources -- not just PDUFA fees, user fees, but other funding from the -- from the government to make sure we're able to meet the need and solve these diseases for patients who are -- have no treatments currently.

Geneva Overholser:
Right. Thanks. Dr. Tellier?

Jean-Christophe Tellier:
I would like to echo what has been -- what has been said before. You know, as a -- as a biopharma company, we need -- we need to strengthen our link with all of the different partner involvement, particularly in this moment where there are so many things that are changing right now. We have been in a model which was mainly sequencing, you know, moving from research to development, then to engage with the agencies to try to understand what would be the framework where our drugs can be used, and then putting them to the public, trying to reach the patients, and if you think about what it is now, it is an evolving environment. There is a lot of new opportunities, and you mentioned gene editing, just for one.

So, the way we're entering research, the way we are translating -- we are able to translate this research into medications, and the way we could be able to have more precise medicine for a more well-defined group of patients requires much more than just a few clinical trials. So, we need to embrace the cycle, to live in a continuous way to try to develop ability to learn life and to connect with agencies to make sure that all of this data can fuel the better knowledge of the medications so we can have a better solution for each of the patients.

So, all of that's required better connections, and so we need to get this openness and these communications, making sure that we are sharing the data at a very early stage and trying to better understand how we can get there.

Geneva Overholser:
And Representative Mfume.

Kweisi Mfume:
Thank you. I want to first of all be very supportive and comment Dr. Califf for the approach that he's making. The outreach is extremely important, and I'd like if I could for a minute maybe to talk about a couple of the real practical challenges that I'm sure he knows are out there for the agency but also for the future of the agency. The number one thing is money. I mean, I don't know how we have any argument about sustainability or progress into the future if we're not finding a way to advocate for the dollars that are needed, and that, unfortunately -- or fortunately, depending on how you look at it, is

hitched to a very political environment that, you know, kind of goes with the way the wind is going every four years.

John Porter, our chair, and Mike, who is a member of the board, and I all served in Congress together at a different time, and I'm not going to suggest that the issues are different for the FDA. I think that there is a lack of willingness to cooperate on basic, fundamental things that in this instance -- the deal with medical science that has really slowed the pace and made the challenge much more difficult.

And then, you know, you've got the fact that the FDA today is not what it was 110 years ago when it was founded. I mean, it's a completely different universe that it orbits in. People can organize almost instantaneously overnight if they hate something that the FDA is doing, if they want to change it, you know, so when it comes to the issue of medical therapies, you see instant groups of large advocates forming all over the place, bringing pressure on the people who make the votes and who matter in some instances that the FDA is not doing enough.

And then on the other side of that is the large population of individuals who are the detractors that say, "Wait a minute. They're just not doing what they ought to do," and some of you will recall a controversy around medical devices -- of a study -- it was completed a few years back -- that said most of the recalls of those devices in many instances had gotten prior approval from the FDA, and so that group is arguing that the FDA doesn't do enough.

Those arguments are going to go back and forth. I think that's good. It's a healthy debate. It causes people to listen, number one, who were not paying attention at all, but there's got to be some effort, in my opinion, to be able to influence the influencers so that the issue of money becomes less of an issue. User fees are fine, but they will never pay the cost. The workforce issue is a real issue, but it really can't completely be settled until you find a way to be able to pay for the workforce and all that goes with it, and so I -- you know, what alarms me is that you have members of the House and Senate, some of whom feel very strongly and are very supportive about the FDA going forward, and then you have others who have no idea other than what they read or heard on the news or someone said to them about what's really happening with the FDA, why it's important, why 110 years later we've got to adjust our approaches and our support and even our criticism in some instances.

And then there's a whole other group who will take the oath of office in January who never had this come up on the campaign trail at all. It's not an issue, you know? So, they come in not -- knowing less in many regards. So, the advocates, I think, have to be reached in such a way that they become real advocates for the agency beyond what all of you in this room have done so many years in your various roles in academia, medicine, and elsewhere, and for me I just think that's a very real, practical challenge that we've got to overcome.

Geneva Overholser:

Well, thank you all. Dr. Califf, I know that you can't address pending legislation, so I want to stick with some key themes -- although the rest of you should feel free --

[laughter]

-- themes that are prominent in the user fee and Cures discussions, and they're prominent because they're top of mind for patients and researchers and others outside the research community. So, one of them, obviously, is the use of real-world data to supplement -- this goes back, Dr. Tellier, to some of what you were saying -- supplement and in some cases substitute for gold standard, randomized,

controlled clinical trials. I'd like to hear from any of you who want to talk about this. What is the greatest opportunity here, and what's the greatest challenge? And anybody who wants to jump in is welcome.

Robert Califf:

Well, let me set the pace here. Just -- I think -- I don't blame you for the way you posed the question. It represents the way most people talk about it, and I think it's a total misfire, and we have a series of writings that are about to come out about this, but there's complete agreement inside the leadership of the FDA that what we're really talking about here are two dimensions of information. One is where does the data come from, and there's a reason -- there's a reason there's a long tradition of doing clinical trials in a rarified, set-aside research clinic environment because there's no way to do the trials in practice because there were no information systems in practice where you could do it, and so, you know, I call this a parallel universe, which is what you're referring to as a classical, gold standard, randomized trial.

What it really is, is a historical, traditional, randomized clinical trial, but that rarified research clinic environment is a source of data. It's not the method of randomization, and so you then say, "Well, we can now expand into clinical practice," and, you know, it took me a while to catch onto this because I grew up developing therapies for heart attack. Well, you can't take a heart attack patient off to the research and say, "Why don't you have your heart attack tomorrow. We'll make an appointment" --

[laughter]

-- "in the research clinic." They come into the emergency room, and that's where you do your clinical trials in real life, and so that's becoming more and more feasible because we have information systems in hospitals called electronic health records now. They're getting better and better, and a lot of what Joe Selby and PCORI are doing -- the NIH -- what it's collaborator is developing -- higher quality, cleaned up data.

But now we have a sort of emergence that we couldn't have even talked about five years ago of personal devices and social media, so if you talk about problems like movement disorders, there are a lot of people who believe that the old-fashioned clinic detail assessments are just completely the wrong way to do it. We should be measuring motion in real life, which is entirely feasible. It couldn't have been done without cloud computing, etcetera. That's all possible now.

That's the source of data. The other dimension is what's your experimental method. So, it's not one versus the other, and I'll just say the highest form of the art in our view is randomization within the real world, and it's happening. There are many successful examples developing, and so if you come back to us and say, "What should go in a label for a medical product? Instructions for use -- what are the risks and benefits?"

In the past, we've been limited by if you do a trial in a research clinic, you don't really know. You can extrapolate, and in general you're right, but if you do, the trials in the real populations who are going to get treated and you measure the real-world outcomes, then you have a profile. It gives you much better information to go into the labels. So, that's the way we see it. This is going to be a rapidly growing area, and we think that the old-fashioned, traditional clinical trial in a research setting still is going to have great value for early development phase two, for many things in phase three, but we also know that, you know, the need to know beyond just getting on the market, particularly with the rare diseases,

where by law and appropriately we're going to use unvalidated biomarkers and accelerated approval to put treatments on the market if there's no other treatment and it's a dire disease.

We've got to then fill in, and by law we also -- then, the company has to prove that the clinical effect is actually there, and, you know, these things need to be done where the patients are in the real world. So, again, I just think it's a false dichotomy of these things. There are two dimensions, and there's a right mix of these two dimensions for any question that you have.

Geneva Overholser:

Very interesting. I appreciate that, and I do want to get to open next and to orphan drugs and rare diseases, but before we get there, are there thoughts in response to this question from others on the panel? Dr. Tellier?

Jean-Christophe Tellier:

Yeah, I know I do appreciate very much the approach because if you think -- once again, if you think about what was the sequence of events before, we get these -- we got this very well-structured experimental environment, you know, that you test what we thought was the best way to evaluate the activity of a drug, and then the drugs come to the reality that it was basically safety elements and the lifecycle elements, and I do think that the emergence of big data in any testing sense and the ability to get all of the data together will help us in two ways. One is with the -- to get better signal earlier in the sense that we would be able to understand better what will be the hypotheses that then we will be able to test, and downstream being able to test them in the real environment, which will be much more powerful to some extent than what we have today.

The other element is will we get also some insight of that, and hopefully we will be able to better connect that patients back to the science. Being able to better understand what is the reality of the -- of the patients living with these severe disease and long term and the ability to better understand the impact of drugs should get us much more insights to be able to connect, through genetics, through human biology, the patients back to the science and so build new hypotheses that can reach to signaling on early clinical developments, such as phase one and phase two. So, we should be able to get a much better sense of this virtual cycle in the future than we have in the past.

Geneva Overholser:

How far away is that future?

Jean-Christophe Tellier:

I'm optimistic by nature, so --

Robert Califf:

Well, I mean, I think if you -- like at the Cystic Fibrosis Foundation, the future is here and now.

Jean-Christophe Tellier:

Yeah.

Robert Califf:

Yeah, I mean, you know, if you want to take care of people with cystic fibrosis as a doctor, you've got to enter your data into their database, which is continuous and ongoing, and most of the patients have volunteered for their samples and data to be available to scientists, and they're looking for researchers to answer their questions, not the other way around, and, you know, I see Victor [spelled phonetically]

here, though -- as the National Academy of Medicine has worked out all the theory. Now, we just need to implement it on a broader scale.

Geneva Overholser:

Did you say something, Dr. Parikh, and then I want to go to Dr. Kakkis --

Sudip Parikh:

Just very briefly my thought here is that this is a case where the regulators, the patient advocates in the industry are actually -- they're pretty close together and it's just a matter of codifying it by Congress. So if we just move I think that's the key.

Geneva Overholser:

Sorry, I mispronounced your name: Parikh.

Sudip Parikh:

Parikh.

Geneva Overholser:

Thank you.

Sudip Parikh:

Sure.

Emil Kakkis:

I was going to say one thing about real world evidence. I think one of the things in the rare disease world is we construct these trials with these very heterogeneous patients and they become somewhat contrived experiments where we're looking for a particular patient, a particular end-point, and they become very narrow kind of views of what's happening, but in the real world we're treating a wider variety of patients in different situations and so -- and the -- and the situation in the real world, the doctor of example giving a drug might titrate the dose and look at the safety and look at what's going on, whereas in a randomized trial they're randomized to a dose, they're at that dose, they stick to it and they have to stick to it for six months even though in the real world, looking at the patient they might have done something.

So there's a lot of things about the two types of information that are different and I think in the rare disease world, when we get approved I think, you know, there has been a lot of flexibility in what we need to get approved and if we are getting more approved on [unintelligible] approvals with biomarkers, which I think is a good idea, then I think we should -- we definitely have to continue to follow those patients along and really collect that additional real world data to help support what's happening and plus I would say in the rare disease world the first treatment out is not going to be the end of the game. It doesn't end other development; in fact usually engenders more development so that we -- as we get out there and collect real world data, we also know what's not really working. We proved it on a particular indication, but what else is not happening in these patients? How do we fix that and how do we go back in an iterative process and I think that's where real world and clinical trial data can speak to each other and help optimize what we get for rare disease patients.

Robert Califf:

I don't want to be too strong here, but we're going to have some arguments, I know, and it's fine.

Emil Kakkis:
[laughs]

Robert Califf:
But --

Geneva Overholser:
I hope so.

Robert Califf:
-- I mean the fixed-dose clinical trial is just one type of clinical trial.

Emil Kakkis:
Yeah.

Robert Califf:
There are other types and if you look at "Oncology Today" and what's being discussed in the Moonshot, it's really just what you described: iterative combinations and dose adjustment in adaptive clinical trials. So that's why I think it's so important that we talk about where does the data come from and what's the experimental design and there are a lot of experimental designs involved, you know?

Emil Kakkis:
There are; it's just when you don't have very many patients, it gets hard to --

Robert Califf:
Fair enough.

Emil Kakkis:
-- make it work. That's the challenge.

Geneva Overholser:
Speaking of patients -- excuse me.

Emil Kakkis:
[affirmative]

Geneva Overholser:
These -- we have these very optimistic thoughts about patient engagement and data and precision medicine that seem very promising, but do we have a challenge in being sure that wide swaths of the population are not left out? I mean, we've seen in the past or see now that that often happens.

Kweisi Mfume:
Well, I think we do and that's why I wanted to go back briefly to this global standard of a clinical trial. I mean the great challenge there historically has been the challenge of making so sure that they are inclusive racially, ethnically, and otherwise so that we don't keep getting results on the end that are skewed to some extent, causing the process to start all over again. I'm not opposed to them, but I think walking into that, you've got to walk in with the sense that the demographic makeup of a population and of a process itself has to be so representative -- representative, let me say that --

Emil Kakkis:
[laughs]

Kweisi Mfume:
-- that it creates for you --

Emil Kakkis:
[laughs]

Kweisi Mfume:
-- a better end-product; I mean it gives you data that is much more accurate.

Geneva Overholser:
You see hopes for that in the legislation now before Congress and in other steps, or?

Kweisi Mfume:
I do. I think there are a lot of people who bring up this conversation more readily and not just assume that there are quote clinical trial police out there that are going to do the right thing and so the conversation comes up on the front end. I can tell you that there has been, at least in some population groups and I can speak for the larger African American community, after the 1934 U.S. public health situation with the injection of syphilis in a population group of men, historically there's always been a, "I don't trust them, I don't believe it, I don't want to deal with it," kind of attitude. So that's not predominant today, but those things cause people to pull back and so I think on the research side we've got to be more aggressive, not to skew the data in any wrong way, but to make sure that there is inclusiveness in the process -- in the attempt to have more accurate data in the end.

Geneva Overholser:
Do others have thoughts about that issue?

Emil Kakkis:
I think one of the challenges we see with getting more inclusiveness is that there's a lot of restrictions on what we can do to support patients enrolling in trials, like how much we can pay them to be involved and they have to take days off work and what we generally find is people that are already financially at the edge can't afford to be in a trial because they can't take the day off work and we can't pay for that and they can't afford to come in and all those rules actually make it hard for people at the lower socioeconomic level from actually participating, and I find that strange that we'd set up a system that -- which would prevent, you know, the coercion of payment, but at the same time we're actually putting a significant financial burden on patients that participate in trials that we do that involve a lot of visits, a lot of coming downtown, a lot of days off work and we don't compensate for that. I think there are some rules need to be changed there so they're not having to sacrifice so much in a way that's really not feasible for them.

Geneva Overholser:
Is there any potential for changing those rules?

Emil Kakkis:
Well, we can for example pay for someone's lost wages, but that's a big deal for people who are living moment to moment.

Kweisi Mfume:

But we can't also assume that most of the people in that group are working minimal jobs; many are on unemployment. I mean it's vast unemployment and so for those individuals to participate it's actually a plus because they're being reached, they qualify, and they're being paid. So I do hear what you're saying about large numbers of people at the lower end, if I can use your term, of the socioeconomic scale that have jobs, who can't afford to take time off, but I would probably suggest for every one of them, there are five others who aren't working at all, who in fact could be a part of a clinical trial if they met every other test. We just have to, I think, look differently while at the same time pushing your argument, because it's a legitimate argument that if you want us to go do this, at least give us the resources to be able to compensate people, which gets back to this whole money issue again that the FDA faces, so.

Robert Califf:

I mean I think if you look at the NIH numbers now, they've essentially fixed it by requiring that people have representative trials and people have figured out how to do it, but most of those are not dealing with the rare diseases where you have to look at each patient one at a time as opposed to larger populations of patients and, you know, my hope at the FDA is that we will have a standard segment of clinical trial protocols -- there's at least a rationale for the approach to inclusiveness, remembering that -- hate to have to say this, but we're only four percent of the world's population so on a global medical products development market, the exact dynamics inside the U.S. are not the only thing that companies are dealing with, and we don't have command and control like the NIH has when it gives out a grant. It says, you know, "You have a set of rules you need to adhere by," but we're working on methods to improve inclusiveness in industry-funded trials.

You know, just as a -- just as a way to illustrate how complicated this can get: simple things like -- we think about Hispanic and ethnicity as a key factor, but when you say "Hispanic" in a global trial, the Europeans are scratching their heads like "What are you talking about? This is just an American issue, not an issue for the rest of us," so it's not simple, but it's a definite issue that we need to deal with.

Geneva Overholser:

Can we talk for a moment about making the best use of the breakthrough designation program or more broadly how to speed solutions for unmet medical needs? Is that something Dr. Tellier would say something about?

Jean-Christophe Tellier:

Well, I mean, yeah. I think it's a very important opportunity because it's -- if you link that to the result and if you link that to the value, the breakthrough initiative have a very noble objective, which is making sure that we can provide at earlier stage, a solution for patients that today have no solutions at all. So I do think that, from that extent, this is a very important priority that we need to -- we need to focus on. It's relatively unfair in a sense to think that we need to get a perfect set of data to look at very long-term if the patients today have no other solutions. Now, the key question is how to continue to engage this dialogue to make sure that when we get access to these opportunity we can evolve and learn as much as we are doing in order to making sure that we do not, in a sense, trade off quality versus time or speed.

I think it's very important. I think the -- once again, the availability of the data, the quality of the data that today are open create much more opportunity to get a very good and strong signal at the earlier stage, that can allow us to engage the dialogue earlier and to get this process faster. It doesn't mean that then we don't -- we cannot do anything after that. We need to continue to make sure that we are

providing data to fine tune and narrow the corridor for certainty of risk moving forward, but understanding the trade between the tradeoff and the balance between the risk and the need, which some of the disease are critical for, versus what we can afford and when, is a very important element there.

Geneva Overholser:

Dr. Parikh, did you want to add anything to that?

Sudip Parikh:

I think that lays out the points very well. My only comment is that this, just like real world evidence, goes back to risk-benefit and this is always the conundrum with FDA and doing that in the right way.

Emil Kakkis:

I think the breakthrough therapy program has been really enormously successful and I think particularly in cancer where there's been a lot of -- where the breakthroughs get pushed and the all hands deck effort -- FDA then moves things forward and gets things happening and a company I'm with got a designation recently for [unintelligible] rare bone disease and the good thing about that is that it's a devastating disease, but not a life-threatening and yet I think it was -- you know, applaud the FDA for recognizing it's still a terrible disease and the treatment mechanism, you know, was a breakthrough strategy and it's having important effects on those patients and we think that kind of view, this, "Let's accelerate and get on these cases of things that are actually going to really change health in a big way," is a great step forward and I think it's worked really well.

Robert Califf:

Three very quick points on this; number one: we have to realize that if something moves to the top of the stack, something else is not going to get done. I used to have a mentor where the fellows knew that he only read what was on top of his pile on his desk, so we'd see who could stay the latest to put our stuff --

[laughter]

-- on the top.

[laughter]

We do have fixed resources, that's a fact, and then, you know, it also emphasizes the need for really smart people at the FDA because the decision on whether you get to be breakthrough is a subjective decision, as you just pointed out and I think the decision-making process at the FDA is the fact that people, you know, aren't absolutely screaming all the time is that -- because it's so important, it's good evidence that we're doing a pretty good job with it and that it's a good process, but I'd also emphasize again, it's critical that people realize that even today with all the hype about how great we are at targeted therapies, over 90 percent of drugs that get into phase one don't make it to market because they're either not effective or there are unknown toxicities or there's a problem with manufacturing that can't be fixed. So when we rush, we are taking a greater risk that one of those ones that would cause harm gets there and we've got to have a system throughout the continuity to measure that. It's a point everybody's made.

Geneva Overholser:

So, you promised that we'd talk about gene therapies. We have about two minutes' left; that's really

adequate for gene therapy [laughs], isn't it? Can we at least address it to the extent that we can talk about whether the existing regulatory regime is robust enough or whatever aspect any one of you might pick up and then we need to move to questions? Sorry to make it so brief.

Robert Califf:

Well, just to make a quick point and I'm deeply immersed in this now because it's moving so fast and we haven't talked at all about food, but remember that's a very large part of the FDA and --

[laughter]

-- you depend on it every day.

[laughter]

Believe me, the food you eat is safe because of FSMA and the system that's been built, but just like you can change genome in a human, where there's been a lot of talk -- it is a simple thing to change a base pair, you know, delete, add to, or substitute, you can do either of those three. A high school student can do it now in a science fair, and so how we're going to deal with that -- you know, the amazing opportunity in food is, you think about the inefficiency of the low-quality food that tends to dominate now, we can reverse that. It's within sight that you can add the most nutritious things to food genetically, I think fairly easily in the future, but that brings up all sorts of issues that regulators and society are going to need to grapple with.

Then let's go to animals, you know? Scientists, you know, have been dealing with -- I mean how many cancers have been cured in laboratory mice and rats, but now you begin to be able to create animal models of human disease actually by inserting parts of the human genome that create the attribute that you're interested in so you can directly develop therapies. This is going to be huge for rare diseases, as you well know, but beyond that let's say you like really lean beef. You can create a whole herd of cattle that are very lean, pretty easily and with the driver in sequence now, you can do it so it shows up in all the progeny. That brings up whole issues about can we get rid of entire groups of mosquitoes? You talked about that earlier today and if you did, what would be the ecological effects and then you go to human disease, you know? We're talking about sickle-cell disease; what if you could just replace the devious mutation? You could do away with this horrible thing that happens with pain crises and problems that people with sickle-cell have, but we don't really know right now how to measure off-target effects when we go to change a human genome. So that's the quick run through of what I've been learning in the last few --

[laughter]

Robert Califf:

Does that give you a little to think about?

Geneva Overholser:

Thank you so much. Yes, indeed --

[laughter]

-- it does and we are now ready to start the Q-and-A. Please wait for a microphone to come your way. How about right here?

Male Speaker:

Well, I'd love to follow up on that topic but I don't think there's time, so let me come back to real world evidence. I think it's a useful distinction to talk about and thank you for talking about where the evidence comes from as opposed to how the study is designed, but that leaves an important part of the question unanswered by this panel. So we've heard, yes, controlled trials done in a more real clinical setting, that's highly desirable. What the advocates of real world evidence though often are talking about is the ability to use other than controlled trials, based on large, electronic databases with new technologies for propensity scoring and adjusting and the like, to draw conclusions in lieu of clinical trials and, you know, the FDA always has accepted data, you know, spontaneous reporting of adverse events and whatever.

I wonder, you know, what -- and this isn't just for Rob, I don't want to just put Rob on the spot -- what is -- what's the thinking about are there opportunities to move beyond spontaneous reporting into more med -- given how many questions we face and how limited resources are, patient resources and cost and whatever for -- and I -- Rob's been a great pioneer of addressing some of those issues and of doing clinical trials in the setting, but is there a space for studies other than randomized trials to really start addressing more of the serious questions we need to answer?

Geneva Overholser:

Panel?

Robert Califf:

The short answer's yes.

Male Speaker:

Yeah.

[laughter]

Robert Califf:

And in fact, you know, I do -- I'd be remiss if I didn't mention devices -- by the way and some people know it, but Jay and I used to be on the other side of the fence with each other, arguing when I was working in the early days of heart attack treatment. He was at the FDA and we were -- had many interesting arguments, but the short answer is yes and if you look at devices, many devices are approved based on a registry and if you look at cancer today with the record number of approvals, a very high percentage now are based on single-arm trials. As a cardiologist, I don't think as these as trials; I think of them as registries because a trial to me should have a, you know, pre-specified control group that's measurable, but we are there, but we don't know where the boundaries are. So it'd be great to hear the other panelists think -- talk -- you know, hear what you think.

Geneva Overholser:

Quick responses from others? Dr. Tellier?

Jean-Christophe Tellier:

No, I fully agree. I mean maybe two additional comments on Jay's questions. The first one is I also do think that there is a tremendous value about sharing more data than what we have today. I mean today we are thinking sometimes in silos and some of the previous panels mentions the opportunity of sharing much more data in order to get access, real life, to a lot of different things and understanding who owns

what. I do think that there are data available right now. I mean in some European countries -- I was in Sweden last week, for example, and if you ask the Karolinska Institutet, they have completely changed the way they are -- they are managing their data and understanding longitudinally, you have here a source of observation that you can have real life quickly. So I do think that the ability to understand how we can leverage data from each other, put that together -- because in the end what's create the value is the question that you are asking, is the ability to build, link and dots, and not necessary just to get the data.

Sudip Parikh:

I think it -- I think it's an evolving answer, right? So we're still learning what is possible and these systems are changing, they're changing from two years ago to today to what they'll be two years from now and so it's a -- it's hard to give a hard, fast yes or no. At least you said preliminarily yes, but I think it's very -- it'd be very -- it would be disingenuous to say yes or no specifically. My concern though is the quality of this conversation is very high; when I get to the quality of the conversation in the Capitol building, it's very low and --

[laughter]

Robert Califf:

You said that, I didn't.

Sudip Parikh:

I did. I'm sorry.

[laughter]

And to give you an example of this, you brought up this animal-human hybrid thing -- just let me have one little anecdote here: I used to work in the Senate on the preparations committee and I had a -- there was an amendment on the floor of the Senate to ban animal-human hybrids. This was in 2002, and I was called to the -- to the floor to go talk to somebody who's on the side of not banning this and I talked about recombinant DNA, talked about genetics, talked about whatever I could think of. He said, "That's great. Tell me something I can understand," --

[laughter]

-- and so I said, "Well, it bans the use of a -- of a reproductive test where you put an animal -- a human sperm with a hamster egg," and I was really excited, I was two weeks into the job and I thought this is great, I'm advising the Senate, and the question I got back was "What's a hamster?"

[laughter]

Geneva Overholser:

Oh, no.

Sudip Parikh:

-- this is where the -- this is where the quality of things is.

Male Speaker:

Yeah, yeah.

Geneva Overholser:
On that note, we must take another question [laughs].

[laughter]

There's one over here. Can we get a mic? We have --

Male Speaker:
[laughs]

Male Speaker:
But he didn't say, "What's an egg?" so --

[laughter]

Male Speaker:
[unintelligible]

Sudip Parikh:
He knew that, he knew that.

Male Speaker:
[unintelligible]

Geneva Overholser:
Yes, please.

Cindy Pellegrini: Well, thank you for a great panel. I'm Cindy Pellegrini] with the March of Dimes and one of the issues that we're hearing a lot more about in our community is the fact that while we have made a great deal of progress in the last decade or more in broadening research to include people of all ages, men, women, people of color, children, the one group that we still systematically, methodically exclude generally from research is pregnant women and there's a growing sense that perhaps we're doing a disservice because these women are taking medication and they do use devices, but we aren't increasing our knowledge in that process. So could you share a few thoughts about the -- how we might move toward the appropriate, ethical inclusion of pregnant women in some clinical trials?

Geneva Overholser:
Interesting.

Jean-Christophe Tellier:
I can.

Geneva Overholser:
Yes.

Jean-Christophe Tellier:
I mean we have a very concrete example of that and actually it's a very good example also of dialogue and openness with the -- with the -- with the FDA. We have currently two clinical trials running, right

now, on the pregnant woman with very specific questions on testing, if the usage of one of our product will have an impact on the babies and trying to get these answers, and we've been able to do that because we realize first in some of our product we are use in pregnant woman, we get the data, then we come -- we came to the FDA with this data and then we agreed on what should be done and we are doing that. I think it's a very fair question; I think it's not an answer to say no or to say it's not possible because in a sense we leave the reality into a vacuum which is even worse than what we will do.

So, I'm strongly supportive of trying to do what here also -- it can be done if we have the patient's engagements. So for example, it's much more difficult to recruit these patients and we need to accept that and to understand that. It should be an act where the patients understand the reality of what's going on, and it's fair to say in the end of the day, "I don't want to take that risk," but we need to provide an opportunity to better understand what's going on during pregnancy and woman of segregation, in particular, is one of the population that have been left behind and it's really unfair.

Robert Califf:

I'm really -- thank you for bringing that up and you may know Senator Murray [spelled phonetically] has a particular interest in this. I hope -- I would urge you to speak to her right about now --

[laughter]

-- because --

Jean Christophe-Tellier:
Right.

Robert Califf:

Well, if you -- just to put this in perspective, there was a great effort in FDA to fix the labeling related to pregnancy and it was a tremendous effort and we have a beautiful way to label drugs for pregnancy, but it's like a scientist who writes a paper: there's a beautiful shell for table one, but there's no data to go into it. People are not doing the studies, and the reticence is understandable. We have to fix it. Just to get personal, I have a daughter with congenital heart disease; there are tens of thousands of women who were not alive in previous generations, who are now because of treatment. Genetic disease is going to be another example, and we don't know how to treat them. The drug labels all say, "Don't use in pregnancy," because they haven't been tested, and so doctors are having to use the treatment with no evidence, which is the way children were until recently.

Geneva Overholser:

I wish we --

Emil Kakkis:

We have one case -- is there -- one example, I worked on a disease called PKU, Phenylketonuria, which is high blood phenylalanine levels and maternal PKU happens when the mother has PKU and has a baby and that effects the baby and we came across this with a drug called sapropterin or KUVAN that was used to treat -- to lower than blood level and the problem was -- of course is that while we had our safety data, et cetera, that there was a concern that --

Geneva Overholser:

[unintelligible] ask a question?

Emil Kakkis:

-- you know, we hadn't proven that it was safe for a pregnant woman, but PKU itself was dangerous and proven dangerous in a child and in that discussion with FDA, what came out, which is unusual, is that the label does include the teratogenic effects of the disease in the drug label to at least -- so that doctors are seeing the comparison of those two things and we committed to following women afterward to do that, but I think it was a situation where even a small decrease in phenylalanine had a big impact on maternal PKU symptoms in the baby. So it was quite important and we think, you know, the FDA, they are kind of working with us in coming up with a label to at least help inform doctors to make a decision between a disease that causes your baby a problem and whatever the risks are of this drug.

Geneva Overholser:

I'm afraid we have to wrap up now, but I want to thank each of you for just a terrific panel. Please join me in --

[applause]

[end of transcript]