THE BROOKINGS INSTITUTION

NEW POLICY DIRECTIONS FOR BIOMEDICAL INNOVATION

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Welcome and Moderator**:**

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The Brookings Institution

PRIORITIES FOR BIOMEDICAL INNOVATION IN A CHALLENGING FISCAL ENVIRONMENT:

Panelists:

ED PENHOET
Director
Alta Partners

FINDING THE PATH FORWARD FOR BIOMEDICAL INNOVATION:

Panelists:

CHRISTOPHER AUSTIN
Director
National Center for Advancing Translational Sciences

DEBORAH BROOKS
Co-Founder and Executive Vice Chairman
The Michael J. Fox Foundation

ROBERT CONLEY
Regulatory Leader and Distinguished Lilly Scholar
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JOHN MENDELSOHN
Professor, Department of Experimental Therapeutics, Division of Cancer Medicine
Co-Director, Khalifa Institute for Personalized Cancer Therapy
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Closing Remarks:

MARK McCLELLAN
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P R O C E E D I N G S

MR. McCLELLAN: Good afternoon, everyone. Good afternoon. I'd like to encourage everyone to take their seat so we can get started with this afternoon's event. And I'd also like to welcome you all to the Brookings Institution today.

I'm Mark McClellan. I'm the director of the Engelberg Center for Health Care Reform here at Brookings, and it's a pleasure to welcome you all to today's event on new policy directions for biomedical innovation. Today's conference is part of a series of research and public activities that we're undertaking related to biomedical innovation. Some of you participated in our conference in June on the state of biomedical innovation. I'm going to come back to some of the implications from that conference in a few minutes. And we've also covered in recent events improving the clinical development pathway and the regulatory review process, as well as new reimbursement paradigms to promote biomedical innovation and ensure that we're getting maximum economic value from all of our work to improve biomedical sciences and apply those breakthroughs to patients.

Today is another step in that process, and it's a step that is made possible importantly by the generous support of the Irene Diamond Fund. The Fund has made a major gift to the Engelberg Center this year to support the Irene Diamond Fund for Health Care Innovation and the Irene Diamond Fellowship for Public Health Leadership. And so before we start, I want to take a moment to thank the Fund for their generous support and their continued dedication to improving the public health. I expect that not many people in this room knew Irene Diamond personally, though if you look up her bio you may know some of her movies and some of her contributions to philanthropy over the years. But she, in her life and her foundation, has been distinguished by supporting innovative -- you might say her outside the box approaches to dealing with

important public problems, especially public health problems, whether that was earlier on issues related to HIV and communicable diseases and innovative approaches to research in those areas. More recently, issues related to aging and public health. They all have a common theme of trying to take a fresh look at issues that have been part of the public policy debate for some time but where, nonetheless, we continue to struggle.

And one of those areas is biomedical innovation. This should be the century of biomedical innovation, with all the breakthroughs in genomics and information sciences and ways of putting this all together for more precise, accurate, timely, prevention-oriented treatment of diseases, influencing diseases even before they have consequences for patients. But getting from here to there has proven to be challenging. And in our work on innovation, we're trying to look at the whole innovation process, the basic sciences progressing into evaluating of treatments in people, the process for demonstrating the safety and reliability -- the safety effectiveness and reliability of those treatments. And then on after treatments reach the market, to promote their most effective use, to improve health and get the most value for patients.

While there is no question that biomedical innovation has added tremendously to the length of lives, the quality of lives of Americans and people all around the world, we are facing some real challenges as our earlier work and much of the work of many of our participants today has identified. These challenges include the challenges of a constrained fiscal environment where the resources available for all discretionary -- so-called discretionary federal programs, including biomedical research are tighter than ever. They are constrained by some of the issues that we've addressed in previous meetings of our innovation work, such as that June meeting, where some evidence was presented on the declining productivity of private sector investments in biomedical innovation.

And putting all that together means that we are at a very challenging time in turning the promise of biomedical sciences and innovation into reliable, effective, beneficial, and affordable treatments for patients. At the same time, there are some unprecedented opportunities to make progress on these issues. And we're going to start with some of the recent ideas that have been put forward to try to make progress, to try to go beyond seeking more money in a constrained fiscal environment, to changing the way that the innovation process works.

In September, the President's Council of Advisors on Science and Technology policy outlined a number of opportunities to do this. And we're going to use that report as a starting point for today's discussion. Copies of the executive summary of the PCAST report are available at our registration desk out the back, and I hope you all have had a chance to look at it. And you're going to hear more about it from our first speaker. Then, after starting that discussion with the PCAST report, we're going to hear from a number of different perspectives on ways to improve the impact of the resources devoted to biomedical research and innovation. These include some novel approaches being pioneered by some of the speakers who you'll hear from this afternoon, all of which collectively may point the way to some important new steps in the biomedical innovation paradigm.

So we'll begin with a focus on the PCAST report itself, what its key recommendations are, and how they might have an impact on addressing these challenges and opportunities in biomedical innovation. Then, we're going to hear from a panel to discuss ways of extending those ideas. Starting out with the PCAST report, we're going to hear from Ed Penhoet, who was one of the PCAST members who authored this report. He's currently a director with Alta Partners, working on biomedical innovation issues.

And then we're going to hear from a number of different perspectives related to these ideas on biomedical innovation. This includes a panel discussion with Christopher Austin from the National Center for Advancing Translation Sciences at NIH; John Mendelsohn from the University of Texas MD Anderson Cancer Center; Debbie Brooks of the Michael J. Fox Foundation; Robert Conley from Eli Lilly; and Earl Steinberg of the Geisinger Health System. These distinguished panelists are going to help address what they see as opportunities for improving the promise of biomedical innovation. In some ways they will build on and in some ways they might provide some counterpoints to the issues discussed in the PCAST report, but what they all have in common is an emphasis on new ways of going about solving the challenges in biomedical innovation that we're facing today, ways to reduce the time, ways to reduce the cost, ways to reduce the uncertainty, ways to increase the productivity of the biomedical research enterprise at a time when from on both the fiscal side and on the productivity side we really need progress like this.

Today's event is a public event. There are press present with us and the event is being webcast and recorded, so everything here is on the record. I want our panelists, as we get to that in a little while, to be mindful of the time. We want to keep some -- plenty of time for discussion of the key ideas that get brought up. And John Berard, who is up front is going to help us keep on track with all of that.

During the course of this event there will be several opportunities for participation from all of you, and we do very much intend this to be a dialogue-oriented discussion. There are not going to be any PowerPoints presented. It really is about getting some ideas out and then exploring them further, so we'd encourage you to participate, too. There will be some of our staff with roving microphones walking around the room to help you make sure you're heard when you ask the question, so when we get

to that point, just raise your hand and we'll get a microphone to as many people as possible.

So right now I'd like to get us started by welcoming Dr. Ed Penhoet to join me up here. Ed has been actively engaged in biomedical innovation through his entire career. Most recently, as I mentioned a minute ago, as director with Alta Partners, a life science venture capital firm, as well as in his service on PCAST. Ed's extensive experiences also include his role as founder and president of Chiron, as well as being the immediate past dean of the School of Public Health at UC-Berkeley and a member of Berkeley's Biochemistry department. Ed is also a member of the Institute of Medicine at the National Academy of Sciences, and he's authored over 50 scientific articles and papers. So a unique combination of perspectives and background that really makes him the right person to kick off this event today. Please join me in welcoming Ed Penhoet.

(Applause)

MR. PENHOET: Thank you, Mark.

Well, thanks to all of you for coming today. And while we're thanking people, let me thank my co-chairs, Eric Lander, who is a co-chair of PCAST; Chris Castle, who is a physician at the American College of Physicians; and Rick Levin, the president of Yale, all of whom were co-chairs of the study with me at PCAST. And special thanks to Amber Hartman Schultz, who is right back here. Amber is the executive director of PCAST at the present time and did Gilman service on this project.

Much of what I'm going to say earlier in this talk has already been said by Mark, but let me reemphasize a few points. First of all, let me start with a personal disclaimer. As you know, the president has had a number of other things on his mind for the last few months, so we have not had the opportunity to brief the president on the PCAST study. We hope to do that next week at the PCAST meeting upcoming, but as

such there is no official response from the administration to our study.

Having said that, the FDA has been a participant in this study from the beginning at many different levels, and was an important -- actually important source of generative ideas for the study, especially Janet Woodcock, Vicki Seyfert Margolis, and of course, the commissioner herself, Peggy Hamburg. So, the FDA has been a very important part of this, but as I said, we do not have the official response from the president's office because we haven't had a chance to brief him on this report at this particular time.

As Mark emphasized, this meeting is an open meeting, and I want to start again by saying whatever I say today is my own personal opinions. I will read some parts of the report to you and try to give you a sense of how the report came about going forward, but I in no sense represent the administration or the rest of PCAST in my remarks today.

Mark alluded to the economic problem that we're facing. To some degree it has multiple roots as we speak. Part of the problem I think is the current paradigm for drug development has two different sources of cost embedded in it. We are simultaneously trying to develop drugs with new technology and new knowledge and a lot of new information, but that new information is not adequate many times to actually address all of the concerns about a new drug that might enter the marketplace. So at the same time that we're using the new technology and paying for the new technology, we are also using and paying for the old technology, which was essentially to conduct randomized clinical trials and look for outcomes as the gold standard, if you will, pretending that we don't really know very much about how things work. So to some degree the analogy I use is the situation libraries now face. For those of you who fund libraries, you know that we're still paying for books and we are also paying for online

library things. So we've got two costs in the library system; in a sense, we have two costs here.

The total amount of money spent on biomedical R&D in this country is substantial, probably in excess of $120 billion a year, which is somewhat around 7 percent of the total investment in health is represented in this sector. But the funding for the sector is under stress in every single part of the sector. Mark mentioned the constraints on federal spending, which are in front of us and are real. But in addition to that, the pharmaceutical companies' profit margins are dwindling and they have already taken steps to reduce their own commitment to R&D in this field going forward. The biotech community is facing a serious decline in the investment and venture capital as we speak, and so there's much less money coming in to the generative side of this field going forward. And so each of the key components, if you will, of investment in this field is undergoing economic stress as we speak and emphasize the need to me to actually think harder about how to get the net return on our investment. And Mark, I like the word you used, impact of our investment to increase. We simply can't count on spending more money for innovation; we have to get more innovation per dollar going forward.

This room is not set up for slides, so for a scientist like me that represents a problem. I'm always used to speaking with slides. But one graphic. The costs are going like this and the productivity is going like this. It's not sustainable. We have to do something different.

So we tried to address some of these issues in working on the problem with PCAST. We were asked by the president actually to look into the drug approval process at the FDA. It became quickly apparent to us that the FDA was the sharp end of the stick, so to speak. At the end of the day, the up or down decision about a new chemical entity entering the marketplace is made by the FDA, but behind that there is a

whole, if you will, infrastructure of other players that lead to the FDA. And the FDA cannot solve this problem by itself. So the problem is a very broad problem, and as a result, we engage at PCAST a wide variety of participants in our meetings. As I said before, FDA was an important participant. The NIH was present in our meetings. The farm industry was present. Patient advocates were present. Consumer groups were present. Physicians as a group were represented by Chris Castle, one of our co-chairs of the study, but by a number of other people as well. So our meetings were very broad based and we got input from a large cross section, if you will, of people engaged in the health sector.

Several overarching themes emerged as a result of those conversations. First of all, it became clear that better integration of basic science and drug development was crucial. I'm going to return to this theme over and over again because a lot of the recommendations sort of look to things like accelerated approval, special medical use, et cetera. All of those things depend fundamentally on scientific knowledge of the disease that you're trying to address. So the basic science is not something that's necessarily for 30 years from now drugs; it's something that's required in the present cycle in order to make the whole system more efficient.

Let me give you a couple of examples. One was the development of something called viral load measurement as a way to assess whether drugs were useful for treating AIDS or hepatitis. Viral load measurements essentially tell you how much virus is present in a patient's sample. Some very good research by my colleagues at Chrion and by David Ho at Rockefeller University show that the best marker for progression of HIV into AIDS as a disease was viral load measurement, a simple quantitative measurement. Since then, virtually all HIV and HCV drugs have been developed and approved using viral load as a measurement, a simple quantitative

measurement that was easy to do.

Another more recent example was the approval of an inhibitor of an enzyme called RAF in melanoma, which was targeted to a specific mutated enzyme that exists in about half the melanoma patients. Again, a very -- you can assay drugs against this target, know how it works. And those are just two examples, if you will, of the way basic science facilitates the whole process after that.

The second thing is we need dramatically improved performance of clinical trials. The field as a whole -- and it's not every clinical trial to be sure -- but the field as a whole is marked today by number one, poor design; number two, long negotiation periods with the organizations that carry out the clinical trials. Really cumbersome institutional review board procedures which are different for every institution carrying out a clinical trial and take a long time; and poor participation by physicians who actually sign up to do the clinical trials. So overall, we have to work really hard to increase both the quality and the productivity of our clinical trials because this is about where 40 percent of the total R&D money is spent by the organizations involved in that. And certainly the efforts by the NIH and a number of other organizations I'll touch upon later are engaged in that.

Again, we have to improve the use of science in the FDA. This is a theme that comes up over and over. And then finally, we recommend much better clarify and guidance in regulatory regimes. Another issue which bedevils the field in many cases.

So let me read to you a statement of the goal overall of this study, "to double the output of innovative new medicines for patients with important unmet medical needs while increasing drug efficacy and safety through industry, academia, and government working together to decrease clinical failure, clinical trial cost, time to market,

and regulatory uncertainty."

This is a case where words matter. Let me go back to the beginning. Output of innovative new medicines for patients with important unmet medical needs. This speaks to the issue of impact. We are used to just counting new chemical entities approved by the FDA. Perhaps that's not enough. We should be looking to the substance of what's being approved. Are these things really having an impact on health? So I think we need some new metrics for how well we're doing as a field to look at the impact of the new drugs on therapies that get developed rather than simply counting new chemical entities.

The recommendations themselves -- and there are eight of them -- first was to support federal initiatives to accelerate therapeutics. It wouldn't be surprising. Most studies like ours argue for more money for the NIH, but especially for NCAF which is a leading organization attempting to enhance the quality and the scope of clinical trials.

The second one is to catalyze the creation of a broad based partnership to accelerate therapeutics. This is an interesting idea. It's going to be challenging in its implementation, and I will return to it later on in my talk this morning -- this afternoon; it's morning in San Francisco -- but perhaps one of the most important recommendations in the long run. But here again, one of the key elements of the partnership is to identify problems and to use the science and development to better facilitate the new drugs.

A third one is to improve the drug evaluation process, and the first of those is to expand the use and practice of FDA's existing authorities for accelerated approval and confirmatory evidence. Accelerated approval really means approval of a new chemical entity without thorough and convincing evidence that it's either truly useful or safe in broad populations. It depends on the science being developed to allow the agency and the developers of these new medicines to make a reasoned decision that it

makes sense to bring this product to market in the absence of a full-blown clinical outcome study. And again, it's absolutely dependent on the underlying science being well articulated and understood. But this requirement essentially urging the FDA to use this pathway more often also comes with a real obligation as Mark indicated to follow up after approval to make sure the drug really does what it says. A recent example of that was the use of VEGF inhibitors, especially of Avastin in breast cancer where it received tentative approval based on early evidence but then the clinical outcomes remain to be shown. We say the FDA must redouble its efforts to make sure that when it engages pharma partners in doing post-marketing studies that they'll actually have teeth on those admonitions, if you will, and that those studies really are done to follow up. Again, key element in accelerated approval and good science that underlies the system.

In fact, we go further to a new category called special medical use. This is a case where a new entity would be actually approved only for use in a specific patient population, and the penalty for using it outside that patient population would be in some cases severe penalties of one sort or another. Why? Because in current circumstance, if the FDA has reason to believe that a new medicine would be used in a situation which is not its intended use, it's entirely possible that the misuse of a new medicine will actually cause many more problems in a broader population than the population for which it was intended.

And one example people frequently use is obesity. So a drug which might be used for morbidly obese patients who have serious health problems as a result may -- the risk and benefit of using that for those patients may be quite different than for those of us who would like to use it to go to a college reunion in three months. And there's a really important distinction. So we recommend this category, special medical use, to allow the FDA to approve drugs for a specific group of individuals knowing in so

doing that its use beyond that would be severely limited. And today the FDA, if it doesn't have that capability, has to assume it will be used for the college reunion folks and not just for the morbidly obese. So this would help a lot in terms of new approvals by the FDA. Again, it's important that it takes the science into account.

But it brings up another issue. The conversation around safety and efficacy always uses those two words. The public's perception of when the FDA approves something is that it's both safe and efficacious. We urge in several places that the FDA try to begin a dialogue of changing those terms to a satisfactory benefit and risk ratio. The benefit for whom and the risk for whom. Because it's a very different conversation and it's in a sense misleading to the public to assume any drug is both safe and -- most drugs are not efficacious for everybody and they're not safe for everybody. So a better articulation of risk and benefit, rather than safe and efficacious we think would be useful. So communication is an important element of this.

Improving FDA management is another area that we looked into. And, you know, speaking of somebody who ran a biotechnology company for almost 20 years, I can tell you that I hear the same thing from many other people. The most frustrating thing on the part of innovators in the private sector is when the FDA changes its views about what should be done halfway through a study. So we do recommend that the FDA actually appoint a single individual to sort of be the shepherd of an IND through the NDA so there's continuity of communication with the companies throughout that process.

In addition to that, the FDA has a number of internal things which need a lot of work. The IT systems at FDA are antiquated and need to be beefed up for sure, and we also recommend that they appoint an advisory board for medical products to the FDA to get more direct outside feedback to the FDA.

There are a few other recommendations. I think Mark touched on the

final one. Is there a need for new economic incentives? A longer lifetime of exclusivity for orphan drugs. You know, I don't have the full menu. We didn't come up with a prescription except that groups like CMS and others should look into these issues to make sure that there are adequate incentives in place to move forward.

So that's sort of an overall framework of the recommendations. I didn't just go through every single one. They're all in the handout that you have and I hope you will take time to read that report, but let's talk for a few minutes now about what's happening as a result of this and other elements and other programs such as Mark alluded to earlier that are happening.

First of all, what's happening with the FDA? We were really pleased, as I said, to see meaningful, high level participation by the FDA in all of our meetings that led to the report. Peggy Hamburg, herself, participated in the rollout of this report at the national academies now about a month ago, and without embracing every single one of the recommendations, Peggy expressed strong support for the report as a whole. In addition to that, since then Peggy has expressed strong support for the special medical use category which may require new legislation in order that we don't think accelerated approval requires new legislation. There's plenty of legislation in place that empowers the FDA to do that. It's under their control, but special medical use, because of its constraints on how a new medicine would be used, would probably need some new legislation.

She's -- I think the other thing that Peggy -- and this predated our report -- but has strongly, essentially, recommended and taken action on is the development of the field called regulatory science. This is a widely misunderstood term. Nobody's quite sure what it means. People usually try to fit it to their own uses, but there's a clear gap today between basic biomedical research, defining fundamental principles, and the drug

development process where targeted, well articulated, well conceived studies using not just molecular biology but epidemiological principles, the great power in the genomics work that's going on, et cetera, need to be refined and brought forward. And this is the sort of prominence of regulatory science. It's the science required in order to meet the needs of a regulatory scheme. And regulatory scheme is not in a sense regulatory. It ends up being a regulatory scenario, as I said, but it's really what do you need for any reasoned group of people to say yes, it's possible that you should go forward with this new medicine, this new therapy.

So there's a growing -- the FDA has invested in some joint education programs throughout the program to enhance this field and move it forward and a number of other agencies. This is not just a problem with FDA but many other agencies. How you use nanotechnology products. How you use a whole variety of new innovations in our society really needs a structured approach to actually defining the science required to ensure that products have a beneficial risk and benefit to society.

The partnership for accelerating therapeutics is gaining momentum. We're very fortunate that two very important and prestigious organizations have decided to take a leadership role in forming the partnership and in getting it in place. One of those is the Institute of Medicine, and within the structure of the national academies and the national academies separately. And the second is the Howard Hughes Medical Institute headed by Robert Tijan. Both of these organizations have agreed to collaborate. First of all, to assemble working groups to discuss how this would work; and second of all, to actually bring together an organization which could move this forward.

The partnership -- there is a drug forum at the IOM, as many of you know, that deals with some of these problems, especially identifying key needs and opportunities. The vision for the partnership is it goes beyond identifying the needs and

actually serves as an honest broker, if you will, to get people to address these things, to work with various different organizations to move key aspects of this forward in the future.

So in addition to identifying the partnership would prioritize, develop specific solutions and detailed plans, and ensure as the best it can that the projects are launched. So this is an organization which will require a staff, which will require funding, and will require the gravitas, if you will, the various different organizations into doing what -- actually carrying out the work, which the partnership won't be able to do.

So this is moving along well with as well as sponsors as we could hope. The NIH effort -- and we'll hear a lot more about that later today -- and the National Center for Advancing Translational Sciences is moving along well. But it can't be expected to solve all the problems of clinical trials. It's simply -- the whole clinical trial enterprise is much larger than any single organization, even the NIH. But so far a very good start on their part.

And to quote from Shakespeare, "Misery acquaints a man with strange bedfellows." Ten pharma companies have actually formed what's called TransCelerate Pharma to identify and solve common drug redevelopment challenges where the end goal is improving the quantity and quality of clinical studies and bringing new medicines to patients faster. A recognition by the pharma companies. It's a bigger problem than any of us have by ourselves. So actually collaborating together in a pre-competitive way. Some people term the whole effort is, you know, something like Symantec in the semiconductor industry early on. These problems are big problems and will require many people to engage in their solutions.

The FDA and Duke University have founded the Clinical Trial Transformation Initiative to essentially work on the clinical trials part of this problem. They say our current system is too slow, too expensive, and doesn't answer many critical

questions. All of those are true, and so it's really working to improve this. This is a critical issue because the FDA is generally overwhelmed as an agency with work to do. Part of the reason it's overwhelmed, poor quality submissions. People wanting to do stupid things. Even wanting to do good things not well described, et cetera. And, you know, being a reviewer of lots of different things, I can tell you it's a lot harder to review a lousy paper than a good one. And it's a lot more work for the FDA to actually deal with poor quality submissions than it is with first rate submissions which are based on good science, have the straightforward program, easily described endpoints, and a program to put those into place. So it's really a key issue.

And then there are other consortia being formed to move clinical trials more rapidly. One of the leading ones is called I Spy. I Spy is a program put together by the FDA, a group of UCSF, and a number of other institutions to test new drugs in the breast cancer arena. Here all of the infrastructure is put in place. So if an organization comes with a new potential therapy for breast cancer, it can be plugged directly into the I Spy network without going through the entire laborious process of negotiating the terms, dealing with 10 different IRBs, or in some cases 30 different IRBs, et cetera, to facilitate the process as quickly as possible.

We are gratified to see many more strategic foundations really entering this drug development space on a much more strategic basis than they used to. So the Cystic Fibrosis organization, the Juvenile Diabetes Research Foundation, Michael J. Fox Foundation that we'll hear more from again later this morning, have all begun to say, you know, it doesn't make sense for us to fund too much basic research and hope a miracle will happen; we better get involved in the direct process of seeing good clinical trials done and bringing good candidates to market. And so I think this emergence of foundations, not only as a funding source -- they have financial resources -- but as a sort of

independent view of how this should be done is a very important move in our field.

And then finally, health care organizations themselves have to play a significant part in this. We have to make sure that new drugs are used responsibly, whether they're accelerated approval or even special medical use, they have to be used in patient populations for whom the benefit and risk is clearly articulated and understood by the patients. And there's quite some amazing things going on in that space. Some of you -- well, if you haven't seen it, you will. The Kaiser Permanente organization has now collaborated with UCSF to do a genomic study, a SNIP analysis on 100,000 Kaiser patients, many of whom have health care records that go back 25 years in the Kaiser organization. It's an enormously valuable, rich resource of patient information combined with the power of genomics. And I think that this kind of study will lead to much greater understanding of patients. For example, just as one example, people are concerned about statin-intolerant patients in terms of getting their LDL levels lowered. Well, this study would allow you to look at least the genetics and genomics of a large statin intolerant population within the Kaiser organization to hopefully identify some fundamental reasons why those patients are intolerant to statins. That's just one example of how the data could be utilized.

So that program, the data are just beginning to be analyzed from that program, but I think are typical of what can happen now when providers and researchers actually collaborate in a meaningful way to move the field forward.

So on that note I'll close my remarks. Mark has agreed to ask me some questions first and then engage the rest of you further beyond that. So Mark, I guess you're going to come back up here and join me. Thank you very much for your time.

(Applause)

MR. McCLELLAN: We are going to continue this discussion and involve

all of you momentarily while we get both of us connected to the microphones.

I would like to remind you that we are going to ask for comments from all of you in just a few minutes. And Ed, I'll take it that you're sitting a seat down doesn't mean --

MR. PENHOET: No, I just didn't want to crowd you, Mark.

MR. McCLELLAN: You've got a lot of space between us on this.

Let me start out with you did a great job of covering an entire spectrum of issues and the PCAST report and going beyond it, and we're going to hear some more perspectives on these issues from our panel in just a minute. What do you think about the progress that we're making so far? It sounds likes a lot of steps are happening now. Maybe they've been encouraged, energized by the PCAST report. Are we seeing any results yet? Maybe to put a finer point on it, one of the metrics that people track in terms of how much innovation is really paying off for patients is the number of drugs that the FDA approves. And that's not just a function, as you said, of FDA regulatory actions; it's also a function of how productive the science coming in is. And though there was kind of a big downturn over much of the past decade, we've seen an increase in the number of new drugs approved, including the so-called priority approvals for treatments for unmet medical needs in the last year or two. It was way up in 2011. It seems to be on track for a higher level in 2012. Is that a sign that this transition to the new way of doing business is starting to pay off? That some of these steps are starting to pay off? There's still a lot of reason for concern.

MR. PENHOET: Well, both. You probably wouldn't be surprised at that answer. I do think the science continues to evolve. And so especially in cancer now, the ability to interrogate tumors and to understand depthfully the metabolism of tumors and the various factors that are at work that cause tumor growth are leading to a whole new

generation of targeted cancer therapies. So that's an example where the field is moving rather quickly going forward because the tools to interrogate the disease have improved dramatically. And we have one of the leading people in that field, John Mendelsohn, who will be here later to talk about some of what's going on in that area.

In other areas it's very slow. Complex diseases, like Type 2 diabetes are difficult. They're just scientifically difficult, and some of the new -- it's not totally clear that you can link cause and effect as easily in that case of a complex disease as in cancer, as hard as cancer problems still is. So I think the progress is mixed, but I'm optimistic that the field is moving in a good direction. But it requires the science and the clinical work to sort of converge. On the other hand, I think that the overhaul, if you will, of the clinical trials system in this country is just beginning and it's one of our biggest challenges. How can we make it better, faster, cheaper?

And people are beginning to worry about this, which is always, you know, the first step in the problem is recognize you have a problem. The problem exists in many different ways. First of all, many companies now are going overseas to do their clinical trials because of the costs here. Just for your information, a typical clinical trial in the United States now costs more than $100,000 per patient enrolled in the trial. All the costs, all in. It's extremely expensive here, and you know, it also goes too slowly. According to CTTI, 20 percent of the physicians who sign up in a typical clinical trial to do the clinical trial never enter a single patient. So, you know, there a number of problems there that need to be fixed.

I think the partnership idea, the partnership for accelerating therapeutics is a powerful notion, but it has to actually come to fruition. The fact that we have Howard Hughes and the national academies both committed to make this happen I think is a very positive sign.

Peggy Hamburg's enthusiastic response to this report. As I said, Peggy has not stood up and said I agree to every one of these recommendations, but Peggy has stood up and said we believe this is the right direction. We believe that special medical use, in particular, is an important new category that we should explore. Again, based on the limited understanding, I think a number of these things really are happening, Mark.

MR. McCLELLAN: Well, that's encouraging to hear. So let me follow up on a few of those. Let's start with clinical trials challenges. You mentioned the work that Duke is doing with CTTI. You mentioned some of the emerging ongoing infrastructures for clinical trials, so it's not a one-off approach. There are multiple treatments that can be tested on an ongoing basis in multiple centers more efficiently. You also mentioned that NCATS, the new NIH Center, had taken some new steps that you thought were very promising in terms of supporting more efficient clinical trials. Can you say a little bit more about that and then about what still needs to be done aside from -- or maybe it's just carrying out these initiatives further.

MR. PENHOET: Well, Chris Austin is going to tell you a lot about that in a little while. But I do think, you know, first of all, NCATS was controversial in the scientific community. No doubt. Because people saw it as competing for funds for basic science. And so many of my colleagues at UC-Berkeley, among other places, were not thrilled to see a move towards translational medicine.

But I think if you put NCATS in the context of a regulatory science environment where you need to bring good science, you know, a clinical trial is a well-run experiment on human beings when you get down to it. So I think that NCATS is bringing the good science of NIH to this field. It's a little early days I think still to judge NCATS affectivity, but certainly I think the goals are in the same direction as what we're saying

overall. And NCATS can play a very important role.

Personal opinion, I don't know if the NCATS can do this all by itself. It requires, again, an ecosystem, if you will, around clinical trials. The academic medical centers in this country have to buy into this. The whole issue of cost has to be addressed by introducing efficiencies, et cetera. So I think, you know, NCATS can't solve all these problems, but by saying the country's largest organization chartered to solve health problems is making a real effort in this space, I think shines light on it and NCATS will do a number of great things.

MR. McCLELLAN: It is a new direction if it falls -- if the follow-up is as you are describing. We'll talk more with Chris about that.

MR. PENHOET: The follow-up is key to all these things. I mean, I would hate to come back a year from now and see nothing has happened on any of these, which, you know, is unlikely.

MR. McCLELLAN: Well, so moving beyond clinical trials into many of the recommendations that dealt with the FDA, as you said, FDA not as the place where all of these decisions and all of the fate of biomedical innovation is determined, but maybe the place where regulatory science -- I think is what you called it or development science -- the science going along with moving the treatments from early stage testing into instead of safe and effective use, use the phrase favorable risk benefit ratio or satisfactory risk benefit ratio. It doesn't quite roll off the tongue for the American public.

MR. PENHOET: Not even your tongue.

MR. McCLELLAN: Not even mine. So getting that different standard in place for accompanying the regulatory science progress seems like it might be a challenge.

MR. PENHOET: For sure it's a challenge. I think it's a worthy challenge

though. I think to tell the American public that every drug the FDA approves is safe is misleading because they're not safe. There is no such thing as a safe drug. Some are very toxic as we know and have been in use for years, et cetera, and they're only appropriate for use where their benefit outweighs their risks. And so to move the conversation even slightly in that direction it seems to me would be valuable because it will impact the decisions made to actually approve those things for use in our population. If the targeted -- it's the risk and the benefit for whom is the crucial question.

And, you know, I didn't make up the term regulatory science. I think Peggy made it up actually, but there is a new move towards what's called precision medicine using the best medicine for the individual that you're treating. Every physician has tried to do that, of course, but the new tools that will facilitate that are coming along. But inevitably, it will require people to really address more squarely the issue of risk and benefit for the intended person down to that level.

MR. McCLELLAN: Is that a different approach than for the scientific development process? This seems like a big challenge for the FDA to take on on its own given it's just a subject to the tighter fiscal environment as everyone else is and it's facing an explosion along with this move towards precision medicine.

MR. PENHOET: Well, a number of things are happening. We are actually -- we may do a study of regulatory science at PCAST because the term is now being battered about -- bantered about; maybe battered about -- broadly in this town without a clear understanding of what the term means. It's much broader than just the FDA because it's a problem for all new products which require some sort of approval. Whether it's by the USDA, the FDA, the EPA, et cetera, you need to have a body of information which allows you to make a decision about whether this substance is ready for widespread use in our society. So it's an important -- I'm a real believer in this as you

can start to tell. If you want me to give another talk in regulatory science I can do that, but after we do a PCAST report on the subject.

But it's a different discipline than doing basic research. And I think that's what people need to get their arms around. Peggy has been a leader in that and a number of academic institutions. I think FDA has sponsored a graduate program at LSU, if I remember correctly --anybody from FDA can correct me -- one at a university to build a regulatory science department. UCSF is building a master's degree program in regulatory science. So there are a number of academic institutions stepping up to this field going forward. But it's a very different kind of work.

You know, one example, I was a basic scientist early on in my career. Do you know what a basic scientist does when the problem gets too hard? Work on something else. No, it's true. But when a problem in developing a new chemical entity for widespread use in people emerges that's too hard, what do you do? You have to keep working on it. You have to figure out a way to get through the problem, rather than avoid the problem. And basic scientists don't think that way. You don't last very long as a basic scientist if you plug away on a problem for too long without solving. You soon find yourself out of a job. So it's a different discipline. And it's a much more disciplined approach to the science than basic scientists are used to. So it's a real gap I think, and we point that out in our report. There's a real gap here for the professionalism of this work. Science, when it's applied to a regulatory scheme, you actually can articulate -- and FDA is far ahead of most other agencies -- exactly what needs to be determined in order to convince yourself that its benefit and its risk are appropriate to the patient you want to treat.

MR. McCLELLAN: We have time for a couple questions from you all in the audience. There are microphones going around. If any of you have a question,

please raise your hand.

MR. FINNERAN: Hi, I'm Kevin Finneran at the National Academy of Sciences.

I wonder if you looked sort of downstream at the regulatory process. I mean, one of the problems we face is that clinical trials can't possibly anticipate every occurrence that might occur when you go to a larger population. And one of the problems we have is then after something is approved and then we find out a problem, how we react to that and how we adjust to that. And so I wanted to know if you had looked at that at all. You had suggested going out in concentric circles. Broadening populations is one way to introduce things gradually and improve on a clinical trial, but what happens when we do get out there, find that we've made a mistake -- either an interaction or over a long period of time a problem -- are there systems in place to improve that so that we don't just overreact and then make a mess of the system at that end?

MR. PENHOET: Let me try to rephrase your question. If you had asked me instead of did we make a mistake, did we anticipate all of the findings that emerged from a broad-based study in a larger population, we may not have and that's I think the question you're asking. That doesn't necessarily mean it was a mistake to approve it, but it does sharpen your focus on the use that the medicine in this case is put to.

MR. McCLELLAN: And evidence developed based on it.

MR. PENHOET: And so, you know, the example, it's very hard to take a product off of the market once it's out there because many people who took the product believed it worked for them. And, you know, people don't want to hear any more about Vioxx, but there were a lot of people who swore that Vioxx was a better pain reliever for them than any other drug and may have been willing to take the risk of a cardiac event. I

don't want to get into that too deeply. I can see Mark frowning already up here.

But another example was Avastin for breast cancer. There are women today who believe Avastin may have saved their lives or at least extended their lives dramatically, although the data, when analyzed in its fullness, didn't show that for the group patients as a whole. So Peggy made a very hard decision to remove from the Avastin label "used in breast cancer, in advanced cancer." It's really hard to do once a drug is in the marketplace, to take it back off.

And there are other examples now where outcome studies have shown that drugs currently in the market don't have the outcome that people sought for the drugs, and therefore, the basis of approval in the case of accelerated approval wasn't necessarily warranted because of the outcomes. But the FDA faces a serious issue in taking things off the market because a large number of patients actually believe, in spite of the controlled experiments done to the contrary, that the medicine benefitted them.

MR. McCLELLAN: I do want to come back to this topic with Earl Steinberg on our panel in a few minutes. We have time for maybe one more quick question now. Any others?

Well, I'd like to thank Ed for joining us here today. Thank you very much.

(Applause)

A great foundation for the discussion to come. And at this point I'd like to ask our panelists to come on up to the front. And while they are getting their microphones attached, I'm going to do some brief introductions.

As with Ed, you can get a lot more detailed biographical information on all of our panelists from the information in the bios that were included with the packets out front. So I'm just going to do brief introductions here.

We're going to start off from hearing from Dr. Chris Austin, the director of

the new National Center for Advancing Translational Sciences at the NIH. We've already been introduced in Ed's comments.

We're then going to hear from Dr. John Mendelsohn, a professor in the Department of Experimental Therapeutics at the Division of Cancer Medicine, also the co-director of the Khalifa Institute for Personalized Cancer Therapy at the University of Texas MD Anderson Cancer Center. And John's coming off a very distinguished period of leading the MD Anderson Center into some of the new directions that we've been discussing here today.

Then we'll hear from Ms. Debbie Brooks, the co-founder and executive vice chairman of the Michael J. Fox Foundation for Parkinson's Research, which is involved in some of these new partnership approaches to developing new therapies.

Then, from Mr. Rob Conley, the regulatory leader and distinguished scholar -- distinguished Lilly scholar at Eli Lilly and Company, which has been partnering in many of these efforts as well. And then Dr. Earl Steinberg, as I just mentioned. Earl is now at Geisinger Health Systems, where he is executive vice president of Innovation and Dissemination and is focused on the kinds of issues that were the subject of the last question to Ed, among other issues in terms of getting better evidence on innovative treatments and promoting their effective use in practice after they're on the market.

We're going to start off with some opening comments, reactions to the report, and thoughts about best approaches to overcoming some of these challenges in productivity and challenges in funding for research and development from each of our panelists. And then we're going to have some back and forth discussion again. Hopefully, some discussion with all of you as well.

So let me get started by turning to Chris for a few minutes of opening comments.

DR. AUSTIN: Thanks. Thanks, Mark. And I was glad to hear Ed say that NCATS doesn't have to solve all problems. That makes me feel better already.

It's an important point to make for a number of reasons, and you'll hear me coming back to this over and over and over again. NCATS needs to be a catalyst for change for two fundamental reasons at least. One is that it is a very small part of the ecosystem. It is two percent if the NIH budget and the NIH budget is a part of the overall biomedical research ecosystem. So it has to play a catalytic role. However, it important to realize that NCATS is the only organization that I'm aware of which is solely focused on solving some of the problems that we've been discussing today.

So, if you look at each of the folks to my left, they all have a particular disease or a particular area that they need to solve. I mean, John, for instance, is a cancer doc. He needs to cure cancer. Debbie needs to cure Parkinson's disease, et cetera. But NCATS is disease agnostic. It's focused on the science of translation and making it a fully fledged scientific discipline, which it's never been before for a variety of reasons.

And I just speak from my own experience that I've been in probably -- you might think of the big three parts of the research ecosystem that is in a large academic medical center, at a large pharmaceutical company, and now in the government. And it's very clear to me that none of them could do it alone. It's very clear, and I've experienced this myself. Translation is an obligatorily team sport, and this is something that pervades all of the questions in translational science because the tradition by which this work has been done has been done by single investigators or single institutions, and it simply doesn't work that way for a variety of reasons.

I often say that trying to have translation work as a golf game doesn't work. It's a football analogy where you have to have different players of different

positions, and they all need to work together for a common goal. But there's lots of incentives that prevent that from happening. And those are some of the things that NCATS is working on. So it really is focused on translational science and the process of translational research as a scientific discipline in itself.

I think some of the things that you heard Ed say are absolutely true. This connection between basic research and clinical applications is something that is far more potential and real than it was when I was in training 30 years ago. My first grant, probably like a lot of folks, I said was going to cure cancer. That was the reason we were doing it. It was completely hogwash. We were not going to cure cancer. We were studying development in the retina, but we decided that the only way we could get it funded was to say we were curing cancer or had some potential of curing cancer.

But I want to make perhaps an audacious statement but I think it's true, that in the last 30 years, that situation has changed rather dramatically. We really are at a place now where we can frequently make for scientific reasons rather rapid translations from the basic research lab to the clinic. So what often holds that back is sometimes the science but equally often it's the processes that are involved.

So if you look within NCATS, just in the last 10 months that it's been in existence, and this is the seventh week of my being director, so hopefully I can't be held too much for outcomes at this point, but if you look at what NCATS has done just in the last 10 months, it'll give you ideas about what's to come.

So there's -- and I'll just run through a couple of programs for you. There's a new program on microphysiological systems to be able to better predict efficacy and safety in drugs. And this is essentially, instead of relying on animal models for testing of safety or particularly safety but also in some cases efficacy, to be able to develop a cell-based or tissue-based human tissue-based models for that kind of

evaluation.

And that's not only a really interesting scientific enterprise which is focused on one of the main reasons that drugs fail or new innovations fail, but it also is a novel kind of collaboration. It's a collaboration between NIH and DARPA, the folks who really brought you the Internet and the GPS, et cetera. And so it's an organization that IAH hasn't traditionally worked with. If you look at another initiative, this so-called repurposing initiative or rescue initiative you might have heard of, it's a collaboration between IAH and AID pharmaceutical companies taking collaboratively 58 molecules which have failed, not in this case for toxicity reasons but for efficacy reasons they didn't work in their original indication, and making those available to academic researchers all over the company who have novel applications for these kinds of drugs.

So again, a novel sort of collaborative paradigm, a novel scientific paradigm though I think will tell us a lot not only about physiology of disease but also about how to do these things better. There's a program called TREND -- and I'll just give you this one example and then stop and we can talk about other things during the questions -- which is called Therapeutics for Rare Neglected Diseases program. It's something that started about three years ago, and the model or the concept here was that again, this being a team sport, there are going to be folks out in the community, whether in the public sector or the private sector who have perhaps a great protodrug or a great idea for a drug but don't have all the expertise needed. In other words, they can't play all the positions on the football team, but if we could slot them in to a team which has all of these other expertise, we could move these forward -- some of these projects rather rapidly.

And so here's a program that just started three years ago, and it's a collaborative program. It's about 14 projects in it now. Half are with small companies,

half are with academic researchers. Just in the first four years there are four drugs that are now in the clinic from that program, which is a land speed record. And I could tell you why that happened, but essentially what it is is that if you take -- it's an age-old finding. If you take people with complementary expertises for whom the goal is individually impossible and you put them together, often the goal is possible and sometimes often rapidly possible. And that's what we're finding. So then we're taking those learnings, those general systems learnings and feeding them back into the system. So those are the kinds of things we're doing.

MR. McCLELLAN: Great. Chris, thanks very much for your comments. I'd like to turn now to John.

DR. MENDELSOHN: Thank you. Well, it's a pleasure to be here. First of all, I want to congratulate Ed in an incredible summary of a 100-page document that is dense with information. I'm going to look at it through a lens of somebody who is working in the cancer field and trying to develop drugs that target problems in the genome. And really two parts to what I'm going to say.

The first is I'd like to emphasize what I see as four major themes that come out of this very strong report. The first theme is a better balance between benefits and risks. He said it over and over again. Now, if you've got advanced cancer, you're willing to accept risks, but if you're a pregnant person and want a sleeping pill you don't want any risks. I've got daughter-in-laws that won't eat fish anymore when they're pregnant because of what happens with mercury, et cetera. But if you've got advanced lung cancer, you're willing to take a lot of risks. And we've got to build into the system accepting that the patient is the person who can decide on the risk. And giving the drug to a narrow population is very important. The special medical use. The example that was given to you was Vemurafenib for patients with melanoma that have a BRAF

mutation. And the drugs work fantastically.

Now, it turns out that science needs to continue. At MD Anderson, we know that about half the patients with colon cancer also have a BRAF mutation, and we didn't just give the drug to them. We studied it and found it didn't work in colon cancer. So science, clinical science has to dig in and do the detailed work on each step of what we're talking about, and it will be done responsibly, but I hope we can accept a higher risk and get things approved more quickly for people with diseases where there's an unmet need, like advanced lung cancer.

The second theme was improving speed and efficiency. And I happen to chair a committee at the Institution of Medicine that produced a little document two years ago, a National Cancer Clinical Trials System for the 21st Century. WE discovered that NCI-sponsored research clinical trials took two years in order to be activated. The questions needing to be asked change in a two-year period. It turns out there are data -- if you wait two years to start a clinical trial, it probably won't get completed. So we were self-defeating ourselves, and we made a 200-page book of recommendations of how to improve things from all stakeholders' point of view. And I can tell you that now the NCI has reduced less than one year to get a trial launched. And these recommendations -- this was motherhood. Everybody agreed. These recommendations are being put into effect. There were many others we don't have time to go into.

Collaboration is so important, and the report mentions Symantec. Now, remember when the Japanese were eating our lunch on developing semiconductors and *The Wall Street Journal* had articles saying we're going to lose the whole computer industry. And precompetitively, the various companies did this. They got together in Austin and created an entity that would develop chips, and we're still the leaders in it and that is an incredible example of what can be done with the pharmaceutical companies

and academia if you get together. The red herring is also protection of intellectual property and that would take an hour, so I won't get into it.

The third theme was information systems. Collecting data. We're way behind on that compared to, say, the military. If we're going to look at drugs being approved conditionally, we have to follow up and collect data. And that means an electronic medical record that is interactive were we can pull in data on what happens to patients that are given these drugs. It's being piloted in the Sentinel program. It's described in the report. It needs a lot more funding, and it needs a consensus that this is part of the process. It ought to be attached to the bills you send to the CMS, for instance.

This kind of information will not only help us develop new drugs, it will help us make decision support possible in the office. It'll decrease the cost of overhead. It'll support research, and it'll create portability of records when patients have an auto accident and their records are in Louisiana. If we have a real electronic medical record, it not only will help drug development; it'll help patient safety.

And the fourth area that was emphasized was funding science. And I won't get into that because I want to briefly describe what's happening at MD Anderson where I think cancer research is sort of in the frontline for taking the kinds of recommendations that are made here and putting them into effect. We know that cancer is caused by abnormal function of genes. We can sequence those genes now and find it out in real time. In less than a week we can find out which genes that might cause cancer have abnormalities in them, and there are over 800 drugs in the pipeline that attack the products of these genes. So at MD Anderson, we've set up the Institute for Personalized Cancer Therapy. And when I stepped down as the president, I moved into leading that, and our goal is to set up the systems -- and it's really complicated -- so that five years from now, of the 100,000 patients we follow, about 30,000 will need this every

year. We're up to about 1,000 patients a year now. We've set up a trial with an informed consent where every patient coming in who has failed on standard chemotherapy and needs and experimental therapy can get their tumor sequenced.

Now, what are the issues we're facing? Number one, what assay do you do? Are you sequencing specific mutations? Are you sequencing all the expressed genes that we know cause cancer? Are you sequencing the whole genome? There are huge issues that I won't have time to explain to you, but informatics is a big part of it.

The next issue is who pays for it. It's all experimental. It's philanthropy and hospital margins and grants and doing this kind of work is not cheap. Then there's the problem with educating the physicians. The physicians who have been trained in medical schools -- and I'm one of them -- have to relearn how to think about assigning care to patients based prospectively not on just what the tissue looked like in the microscope but what was the genetic abnormality in the tissue? And we have to design clinical trials to take advantage of that. We have to explain this all to patients. After all, they have to make the decision are they going to accept the therapy or not? And I think the exciting thing for me, having been in this field now for close to 50 years, is that finally it isn't cells and worms and fruit flies that are the chief target of research today; it's the human being with cancer and specimens from that patient and some of the best scientists in the world are approaching this. So I'm an optimist.

MR. McCLELLAN: Thanks very much, John.

Let me turn to Debbie.

MS. BROOKS: Hi, thank you.

So I thought I'd start by just acquainting you briefly with the Fox Foundation as an example of one of these nonprofits that is focused on a specific disease area and kind of taking on a new role in terms of accelerating drug development,

and then I'll tell you a little bit about what I'm most excited about and also what keeps me up at night.

So the Fox Foundation started in 2000, and in a town like Washington where most nonprofits are considered patient advocacy groups -- I don't think I'd call us that -- we are 100 percent focused on funding research. And so we really are an aggressive and strategic funder in the field of Parkinson's drug development, and we have funded over $300 million worth of research since we started in 2000. Our program team is a combination of PhDs, an MD, and MBAs, so we're purposely thinking about science and the business of science so that we can position ourselves to put money to work aggressively and develop expertise in addition to the funds available.

We fund high-risk targets, and we move them from preclinical into clinical testing. Not only do we chaperone these ideas -- and since we started we've worked on over 100 targets -- we also are tackling enterprise-wide challenges. So for instance, we've been leading an effort to identify biomarkers, particularly markers of progression so that we can better design clinical trials, and we've been tackling known challenges, such as patient recruitment and participation in clinical trials. For instance, we launched a web-based tool called Fox Trial Finder to try to connect willing Parkinson's patients to needed trials.

We have a different risk reward profile than the other major funders. We're by far the smallest of all of this and the U.S. Government might spend $125 million a year in PD research; we spend about close to 60 right now, and industry we think spends about a half a billion. And so while we're the smallest, we look to complement how our dollars can behave vis-à-vis those other players.

We do get to act with a different kind of urgency. I think that goes along with that willingness to take risks, but we're very focused on efficiency and we certainly

are keeping the patient outcomes front and center. And that's a nice complement to those other two groups given how they might think about use of their capital.

We design our portfolio with milestones, and we're very data driven. And we see ourselves as being in the business of de-risking Parkinson's drug development. So given our size, we don't think we'll ever be big enough to develop, you know, take anything over the goal line, so we can use our strategic dollars to really add dad around existing ideas and really get them to the point where someone else will pick them up and take them over the goal line.

We're focused on disease modification, untreated symptoms, and drug side effects, so we really can look across that portfolio of opportunities that all represent some unmet needs for Parkinson's patients. And as we've scaled -- I think this is the greatest benefit is that we can do more than one thing at once. And so we can really look at all of these unmet needs from the view of a Parkinson's patient and work on as many as possible.

We are funding in the U.S. and outside the U.S. And so we are really agnostic to where the best ideas are. And that gives us some flexibility and also presents opportunity. And I'd say today we think the Parkinson's drug development pipeline is as good as it's been in decades. So I think that's some good news. I'd say the things I'm most excited about are, in fact, that pipeline, which looks exciting. I'm also excited about the fact that I think our -- what we do, which has been described as a model of a patient-led organization -- I'm not sure it's a model anymore. I think actually what we are seeing is that this kind of role is highly complementary to the other, you know, kind of active constituents in drug development when you cross that whole enterprise, and we can provide a role with that patient lens that helps with prioritization of targets, and we can have the long view that really maintains persistent problem solving in terms of the some

of the ecosystem challenges.

Another thing I'm very excited about is the increased role that the patient can be playing in terms of drug development. Certainly, patients funding research, so as we're still a pretty young organization but having funded $300 million worth of research, that's pretty much all coming from the patient population, which is pretty extraordinary considering it essentially didn't exist before.

Secondly, we can maintain clinical relevance, that persistent voice of the patient in the mix. But also I think, and most novel in this area, is the ability for patients to be playing a more active role in the research itself. So moving towards models where we have patients directly contributing data, not just in the traditional clinical research setting which we are trying to boost their participation, but also just in patient-centered research, which can enable us to take advantage of technology advances where we can, for instance, working on a program with a company called 23andMe where we're looking to add significant phenotypic data on top of the genotypic data that's already been collected. And so we think we can really add a significant amount of data to the field.

In terms of what keeps us up at night, I'd say access to capital, not surprising. And in particular, when we see a pretty strong drug development pipeline, we have a lot of novel targets in phase two. And that's good news. The scary news to me is it seems like the goal line keeps moving. We think we're in the de-risking business and thought that if we could get positive phase two data that someone else would surely run with those findings, and what we're finding is that we may have positive phase two data and still no funders for a phase three trial or certainly not full funders. And so we look at that and realize that we need to see what we can do to be raising even more capital, which is already a pretty high bar.

And I'd say another thing that keeps me up at night is even though we all

can spend a lot of time understanding and describing these problems that we see systemically, there is this challenge of the fact that it takes us a long time to get to good solutions means time and lives that are at stake and waiting. And so we really can't let up on the urgency to be tackling some of these extremely complex challenges.

MR. McCLELLAN: Debbie, thank you very much.

Rob.

DR. CONLEY: Mark, thanks very much. It's good to be here. And Ed, thanks for your beginning comments. I really have a lot of thoughts about them.

One thing that's happened at Lilly recently is that I am sort of a new regulatory scientist. I am a physician and a psychiatrist and have worked for many years as a developmental neuroscientist, but in this thought of trying to move regulation into regulatory science, that's one of the things we're actually trying to do is to have more strategic leadership for our group instead of being just sort of transactional working with the agency.

As part of that, one of the things I think about with the PCAST report and some of the things that you talked about, Ed, is that I think it is very important we develop this regulatory system better in the 21st century. And I think about five different areas. One is that we have a timely system now. It's very important that we know with Parkinson's, with many other illnesses, that we really do have a lot of potential leads right now, but part of what we really need to do in science is do a better job of translating things quickly than we have in the past.

One way to do that is the second thing is to make our decisions in the regulatory area, both within companies as well as in our interactions with the U.S. and other agencies more predictable; that we do support that decisions should be based on, you know, sound scientific criteria and that it's very important for innovators to

understand what their risk level is as they go into the process and to not feel like their risks are uncertain. That's one of the things that makes them very hard to move things into phase three trials.

We'd like to see a better consistency across FDA review divisions; that there are some consistent, predictable standards for what good evidence is and hope that we could have some precompetitive, agnostic panels, you know, for what that would be. One area would be in advanced analytics and statistics. You mentioned appropriately that one area where I think our FDA needs upgrading is in information technology. I'd move that even into the statistical realm, and there's been huge advances made recently, but it's very hard as a sponsor to come in and not be seen in a sense as trying to gain the data. If you're trying to move things forward in some new statistical, analytic method that may be very acceptable, but it would be nice to be able to move into an area where those advances are translated better into something that's acceptable and not using older techniques. So maybe another thing to work on would be something like that that we could then all lean on. We want our system to be scientifically rigorous. We think that it's very important to increase scientific expertise within the agency; that we recognize that's something they've been working on very hard, but also do a better job of accessing outside expertise. We think that's critical to have these sorts of exemplary panels about how to actually tackle important disease conditions that the agency can tap into that allows them to apply new evidence standards to very acceptable and transparent to people.

We're hopeful with the PCAST report, with the passing of the new PDUFA 5 regulations, that some progress is being made. We think that with PDUFA 5, that there should be a higher level of accountability and transparency in the FDA decisions. We think it will bring new budget money into the FDA, which is really needed

to help them make changes. And we think it should empower the FDA to focus more on personalized medicine, biomarkers, patient-oriented outcomes; things that we all think are very important to do.

We also do agree -- I very much agree -- that we need to focus on this risk-benefit framework. We'd like to see our FDA and other regulatory agencies have a more systematic transparent way of actually assessing risk and benefit. We recognize that it's very important to understand risk with different medications. We do think that it's very hard, I think, many times to understand what levels of benefits are important. And again, I would say exemplary panels. There's other methods of trying to understand what standard we need for different disease conditions. And if we had a way to better understand, I would say with some rigor what benefit is, that would actually really help us with the risk-benefit equation. Risk is in some ways much easier to quantify than benefit from any disease conditions.

So we also need to do better work in industry and in translational medicine to maximize risk-benefit ratios. Older models are running more and bigger clinical trials. That's not as economically feasible or scientifically rigorous as it once maybe was. It never was better in science but once it's really not in the economic world anymore that we can do this, so we really do think we should focus better on improving individual outcomes. We think we can do this. We have a tailored therapeutics group within Lilly that's really focusing on better phenotypic markers, established biomarkers, innovative biomarkers that allow us to hopefully develop medications that are better focused on target populations where you'll actually be able to expect a good outcome, fewer nonresponders, and people really will be able to get kind of what they pay for, you know, with the medication, with expected benefits.

Finally, we recognize that there's a rapid pace of change right now in life

science, as well as in other areas, and nobody can monopolize all the brainpower you need to be able to keep up with these changes. So we're very much actually in favor of preclinical and precompetitive areas of collaboration between companies.

Ed, you had mentioned -- and I'll look at it because the term is strange to me -- the TransCelerate approach. But one thing that's come out just now from this TransCelerate initiative is that Johnson and Johnson, Merck, and us at Lilly have just announced that we're going to combine our efforts, and we're going to make this go out to the other TransCelerated partners as soon as they're ready to get it into their database, a new database of people and investigators who do clinical trials that allow them to merge their good clinical practice trainings, their kind of IRB connections, a lot of the infrastructure of doing the trial. I mean, again, like a risk-benefit ratio that sounds like a strange thing, but honestly, there's been a lot of bureaucracy that makes people do two and three trainings, the same training over and over again to just have an investigator qualify for one trial for one company versus another. We're trying to simplify that and get out of our own way and use informatics to be able to do it.

And so we do think in summary that we do want to develop better partnerships with others, both academics as well as people within our own community and industry and with the agency. We do very much support the idea of these new centers of excellence or other ways of developing better methods to understand benefit and risk. We do think that it's useful to have better networks of scientific advisors, and it's very important for us to support public and private partnerships. We have done work and been grateful that the Michael J. Fox Foundation exists. We worked with One Mind. We've worked with other groups to try to develop, again, precompetitive space that we all can share data that we've already collected together. We've supported the access for repurposed drugs, and we're in favor of those things. I mean, we do recognize that the

older methods for drug developments really are not going to work in our current economic model, and we can actually do better. We can really do better with informatics that's in front of us and I feel very strongly as a leader of the biomedicines regulatory group within Lilly that we can bring a better scientific focus into a field that hasn't had that rigor. And I do think that's something we need to change. So I'm glad I'm here.

MR. McCLELLAN: Rob, thank you very much.

Earl, we'll turn to you now.

DR. STEINBERG: Well, I'm going to take a slightly different slant on things and the comments so far about innovation, new drug development, the end is not innovation in and of itself; the end is obviously improved patient care. And I want to talk for a bit about things that we can do to improve the quality of care that patients receive given whatever data have been produced. And unfortunately, the gap between what we know to be the optimal thing to do and what patients are receiving is quite substantial. And just as there may be a funding crisis in terms of basic science, we're entering the phase where the funding available for patient care is going to be increasingly limited and we can't afford to waste dollars on therapies that are not effective or are not being used optimally.

In that regard, I want to make one comment about this special medical use which I think is a great idea. On the other hand, I'd like to actually see it broadened in that it's hard for me to understand the rationale for letting physicians use an approved drug in any way that they see fit without any evidence or any science having been done to examine that. In the case of the drug that was tested on patients with colon cancer, at least that was evaluated in the context of a study as opposed to anybody deciding, well, I think I'll try this drug on this. And if we continue the way we are, instead of calling it special medical use, perhaps we should call it experimental medical use outside of an

experiment where it really, I think, is not particularly productive.

I want to talk about a couple of things that we're experimenting with or using at Geisinger that I think will enhance our ability both to evaluate drugs and other innovations as well as improve the quality of care we deliver more generally. The first is the use of natural language processing and machine learning to mine for unstructured data in the electronic medical record and in care management software. There is a wealth of unstructured data that we basically ignore today and there is a considerable amount of research that's been done over the past two to three years to suggest that adding a look at that information will significantly improve our understanding of different diagnostic and therapeutic modalities and improve quality of care.

The second is I want to follow up on the comment on EMRs. Geisinger installed its EMR in 1996, so it was epic install number three in the U.S., and it's got one of the strongest EMR IT teams in the country, and we have, in my opinion, leveraged that EMR technology as much as anybody in the country. In order for a lot of the types of collaborations that have gone -- that scientists would like to conduct across institutions, we're limited by the lack of interoperability across EMRs. So people have been snowed, in my opinion, to think that EMRs are interoperable. Nothing could be farther from the truth. They are completely not interoperable. And the problem can be easily solved by the EMR vendors if they wanted to solve it. And I think that we could do a great deal to benefit the patient care and to science by pressuring the EMR industry to open up the system so that there can be true exchange.

I know at Geisinger, for example, we have scientists who want to participate in a number of multicenter trials, but they're not able to because they can't collect the data the way they would like to -- the way they have to collect it for the clinical trial within the context of our EMR. And this problem could be solved incredibly easily

with clinical apps that operate outside of the EMR, but interoperate with the EMR if the manufacturers would simply open up certain APIs in their systems.

Finally, I want to talk about a number of things that I think ought to be one to improve compliance with best practice. One is we're increasingly trying to use real time data decision support. So these are analytics that are connected to our EMR. They're done outside the EMR but fed instantaneous into the EMR, and our experience with this has been very positive, particularly in one instance in identifying patients who are deteriorating and need to be transferred immediately to the intensive care unit.

We also have been using a variety of advanced data analytics to do predictions. These could be anything from, you know, predictions about which patients are going to be complaint with their medication and which weren't; patients in whom a particular drug may not be safe or may not be effective, and I think there's a lot more that could be done to leverage good databases in that regard.

So I'll stop there.

MR. McCLELLAN: Great. Thanks very much, Earl.

Now, collectively, you all have covered a spectrum ranging from the early stages of moving from treatments in the lab into human testing and the conduct of clinical trials, all the way up through the development process and into more effective use in actual practice with a lot of further evidence development going along with it. So a lot of ideas in there which I hope those of you who are here with us today will also follow up and ask about.

But I'd like to start with a couple of themes that seem to be common to many of your remarks. One was this returning to what was called regulatory science or development science and Ed, maybe you're going to formally define this for us at some point soon. But what it seems to encompass is the goal of getting to precision evidence

for precision medicine. As John said, it's about treating people, not just looking at individual disease pathways. This goes along with the notion of a risk-benefit assessment in particular kinds of patients, but it creates a really heavy demand I would think for relevant evidence and compelling evidence. And you all have described collectively a range of public initiatives, private initiatives, and so forth to try to get us there, but it does seem like it remains a big challenge, especially if you're asking for something of a change in a regulatory paradigm, which is supposed to reflect the best and latest science, which may not be there as much as we'd like for precision evidence relevant to -- and convincingly relevant to particular patients. Are we really making progress on this goal? And it seems like, John, it's very central to a lot of the work that you're doing. And Rob, the new directions that you talk about. So I want to push a little bit more to see if we, you know, can we really get there soon?

DR. MENDELSOHN: Let me push back. Let me just say when you sequence a human genome and you get the readout, if you have the right informatics people around, there's a thousand mistakes just in the technology that have to be corrected for. Then, the fact that you find an abnormality once doesn't prove anything. You have to re-sequence over and over again. You might sequence the same genome 200 times and you still don't have proof that what you find is what's relevant to the patient.

Now, mammograms are wrong 20 percent of the time, but most women get mammograms because they like that added benefit. And I think we're getting back to what risk and benefit are. And a regulatory agency, if it is approached by a congressional investigating committee, which happens occasionally -- you made a mistake and you're on the hot stand -- has to say to itself I'm going to avoid any risk because I don't want to be plummeted by the press that I let something happen that could have been avoided.

And if we try to say we need absolutely proof before we do anything, we're not going to get very far. And this is something that we have to educate ourselves, understanding that there are no risk-free answers. And the FDA, I don't blame them for trying to avoid risks because I read the same newspapers we all do. And if things happen and a drug -- one patient dies, there is a huge outcry. And of course, it's a tragedy. But we've got to balance the risks and the benefits. So I think this is a public education requirement. If we're going to move science along, the people have to understand science isn't perfect. I remember in medical school I was told half the articles I read in *The New England Journa*l were wrong. The data were right, but something hadn't been asked that the investigators didn't know, and our job at medical school is to teach you how to learn, how to decide what's right and wrong 20 and 30 and 40 years out while you'[re practicing. There's no free lunch. So that's an indirect answer to your question.

MR. McCLELLAN: It is. But to just continue pushing, it did seem like you were laying out some ways to get to better evidence relevant to particular patients.

DR. MENDELSOHN: Sure. Sure.

MR. McCLELLAN: And it seems like that would help bring down the tension or the conflict.

DR. MENDELSOHN: Yes.

MR. McCLELLAN: Between the quality of the evidence, the frequency of -- if you don't want to call them mistakes, at least, you know, learning more later that would require -- that in hindsight would have required better decisions. It seems like better progress there would help move us along in this process.

DR. MENDELSOHN: I think we're getting better at it. I think the FDA is getting better at it. I think all of us understand the issue. But there's this fear that we're going to let something happen and something bad will happen to a human being and

we're going to be punished.

MR. McCLELLAN: Any thoughts on better evidence here?

DR. CONLEY: No, I think that's a very good point that you've made because, I mean, to me, I think back to our standards that we had in medicine, like hemoglobin A1C levels or lipid profiles. I mean, things that really are, in essence, they're biomarkers. But they've also moved enough in the medical practice that we understand their sensitivity and specificity problems to a degree, although you also see the field progress all the time. ADA is always redefining sort of what Type 2 diabetes is, but that doesn't become a challenge for improving new drugs specifically because it's sport of seen as an agnostic standard.

So from our standpoint in developing new diabetes medications, the ADA standards for diabetes aren't a problem; they're just a thing. Whereas, when you look at genomics, it's more of a problem right now. So right now, a company trying to develop a genomic-based method for targeting patients, you know, are we trying to develop another test that we're trying to market? You know, again, do you then have to have that perfect level of evidence? You know, what is the level of evidence needed? And what I'm hoping is I think people are trying to push forward, but we can develop some, in essence, better somewhat agnostic to the industry, you know, standards for what genomic evidence is. What is targeted? You know, how much do you need to know about a genome to do better in actually focusing a person's care without it trying being perfect. Just like nothing else is going to be perfect.

DR. MENDELSOHN: And we may have to advise it two years from now.

DR. CONLEY: Well, then --

DR. MENDELSOHN: That is okay. And that's one where as a representative of a manufacturer I don't want it to be a Lilly standard. I don't want it to be

just about a Lilly medication, you know, because that really is intrinsically flawed. I mean, if it's medicine, it really needs to be about a medicine standard. But we're being asked to meet that standard of evidence, not that we're proposing that this is the standard because I would think in many ways it's very fair for society to ask me as a manufacturer representative, well, if you're going to do something that's just going to, in a sense, benefit you, I mean, as much as we say it's going to benefit everybody else. If it's just going to benefit your drug, we want that level of evidence to be perfect. You know, whereas, if it's generalized and this is part of advancing medicine, I think it can change the standard. So I don't, you know, I don't want a standard lowered per se, but I'd like it more realistic. And I very much want it to not just come from the small us but some larger version of us.

MR. McCLELLAN: And this larger version of us, and he mentioned, you all mentioned new kinds of collaboration to develop this relevant targeted evidence using genomics, developing standards to go along with it, that's part of the scientific process. The same kinds of collaborations could help clarify those issues.

DR. MENDELSOHN: I very much would like to have that happen. I mean, that's why I mentioned this precompetitive space work a number of times. I mean, I really do think that collectively, I mean, just again speaking as a representative of industry, many of us have done a tremendous amount of work now in pharmacokinetics. And pooling our work, even in our failed products, would allow us to understand a number of disease conditions much better. And I honestly think there really isn't a lot of resistance within the industry to doing that pooling. I mean, we are talking about precompetitive initiatives all the time now. And we're actually trying to reach out to do that. So I think an infrastructure where that could happen better, I mean, in some ways speaking for myself and then as a representative of just one of the pharma groups, but

there's a lot of interest in that happening.

MR. McCLELLAN: Some infrastructure for better development can come from public support, and Chris, you talked about the role of NCATS and helping to support an infrastructure for more efficient trials, for repurposing of drugs, again, sort of a precompetitive issue that at least recognizes precompetitive by most participants in the industry, but as you said, you've only got limited resources for this. You see yourself more as a catalyst. Are there any -- I know you've been there for, what, all seven weeks, but are there any lessons about what the best way to catalyze -- for the Federal Government to catalyze efforts like these to develop better scientific evidence?

DR. AUSTIN: Yeah, sure. And I think like a good catalyst, it brings together reactance that can be in close proximity but not produce anything without the catalyst. And I think if you listen to the folks on the panel, they're all saying the same thing and yet you can bring them into proximity. But unless you have a catalyst, nothing is going to happen. Sort of like having the bride and groom at the wedding but nobody officiating. You know, nobody's going to end up getting married unless there's something there to actually marry them. And that's to some degree what NCATS will do.

But I think also what I think about from both a preclinical and a clinical standpoint is when I talk to FDA, which I do a lot because they're our sister agency so they're on common e-mail servers so it's easier for us to talk to them, what I'm struck by over and over and over again is that there are many examples where programs come to FDA that are simply not well done. And I'm struck by what happens when FDA has -- and Ed mentioned this -- has a good data package, whether it's Coray for small cell lung cancer or Kalydeco for CF, those reviews went very smoothly because the data were there that the regulators require. And think a lot of the reason for this in my own world, and granted, it is skewed toward the academic and small business side where you have

folks who maybe started out in a different field and now they're trying to do translational trials, they're trying to do drug discovery, and some of the really fundamental things about what FDA requires to have a drug be approved are simply not known. And it's not because they're dumb or they're misinformed; they just don't understand what the regulatory process is.

The other thing that we run into all the time is that in the private sector we have many small companies that come to us for help, and they are so pushed by the short-term imperatives of the market that when they come to us they're going to do some really dumb things. And it's bad science. But they're going to do a Hail Mary pass because that's -- time's running out and they've just got to throw that football. And if any disimpassioned person looked at that project the way we do, they would say the chances of success here are very small. They could be improved but it needs time and it needs resources.

So one of the things I was interested in my help with this -- it's not something NCATS is doing, at least not directly -- but it's this proposal from the MIT group about debt-based financing of new therapeutic development because it has a longer time frame than the VC world, which is typically two to three years. And anybody who has done this knows that that is way too short to really do a good drug development program.

The last thing I'll just mention, because I didn't mention this before, about 85 percent of the NCATS budget is actually in the clinical space. And we are focusing intensely on questions of interoperable informatics platforms to tie these CTSAs together. Common IRBs that would allow review to be done rapidly and then have clinical trials initiated in a rapid way to have technologies which are available and capabilities which are available throughout the network from specialized centers so that each center doesn't

have to duplicate the work of each one and can actually work together. One of the things we're running into in doing that is that the incentive structures are not really well developed for having different pieces of the biomedical ecosystem be interdependent upon each other. And there's a lot of suspicion and a lot of reluctance to be dependent on another entity or another person in order to achieve your goals. Everybody wants to own a complete means of production.

But all you've got to do is look at pharma, who when I was there these were vertically integrated companies that did everything from gene discovery to post-marketing. And you look at their business model now; it's been disarticulated. It's not -- and it's because that vertically integrated model, I'm going to do everything myself, does not work. It's like, again, the football team. Imagine a football player trying to play all 11 positions simultaneously. It's not going to work. And that's -- one of the hard evolutions of our ecosystem has to be to allow that interdependence to happen.

MS. McCLELLAN: Debbie, is one way of look at what you're doing trying to bring these different parties together? Maybe it's not -- it's not just catalyzing because you are providing some real funding for the research and development, but do you have any lessons from your work to help overcome some of these challenges?

MS. BROOKS: I mean, as I hear some of these things, we've been active in dabbling in almost all of them, and so I do think that -- I don't know that a group like the Fox Foundation is going to exist for every disease indication, but in the places where they do I think, you know, that kind of new entity can really bring some needed glue. And you know, I have a lot of empathy for folks in CNS that are trying to imagine how they're going to design a trial for disease modification. It's not that FDA knows how to guide them and just keeps a secret; nobody knows how to design that trial.

So, you know, in trying to figure out how to lead the way for the first

disease modifying drug in a field, that's pretty -- that's a tall order. So, you know, when we look at trying to problem solve across all these constituents, we can at least try to bring capital. We can really be a center in terms of expertise, but we do find that people are willing to come together and roll up their shirt sleeves and do some of this hard work. So our biomarker consortium is a good example of that where we have 13 companies that are cofounding a $45 million, five year study to verify markers of progression. And everybody for years will say, oh, this is needed; this is needed. But, you know, we had to not only be the catalyst but we had to put up at least half the money, and we spent two years getting all the corporate partners to say yes, we're in and we're ready to do it now. But now we're seeing some progress. That study is probably a third of the way through.

So if I look at a different part of our area, something like dyskinesias, which are side effects of Parkinson's drugs, we've really been able to see that field move pretty significantly. And the role that we play shifts as the field progresses. So early on we were funding animal models and trying to figure out how do we look at this in the preclinical space and figure out if they're good targets or good therapies. And now as more things -- actually, we have half a dozen different targets in phase one or phase two, and as those were moving to that part of their testing stage, we sat down with companies who were working the fields and said what do you need next? And at that stage, our role was to validate scales. And so we ended up doing a clinical trial to validate the scale so that we could have each of these different companies working dyskinesia, have a scale that they knew they could point to and that would provide -- and FDA was happy for us to provide that guidance and kind of as an independent group validate that. So I think you can play a variety of different roles as needed, but it's nice to kind of have a group that can, you know, be nimble and move it around.

MR. McCLELLAN: Now, I know we're running a little bit short on time,

but I did want to ask one follow-up to Earl. So let's say that these approaches work. And what will be coming to you and other providers in our health care delivery system are more targeted therapies with more relevant evidence to particular groups of patients, but certainly not all the questions answered definitively. Is that something you welcome? Is that something you work with? Is that something that raises some new concerns?

DR. STEINBERG: Well, no. I would say we would welcome it. And I think that it means that we would adapt our computerized decision support to take account of the increased personalization, but we would welcome it and we would be in the position to collect additional data that might help refine the initial thinking on, you know, which treatments are best for which types of patients.

MR. McCLELLAN: We do have a few minutes for questions. I think the group has done a better job than I could of summarizing some of the main lessons and implications on the way forward. So we're going to dispense with that.

I would like to open it up to those of you who are here. Any questions or comments from what you've heard about these perspectives and new directions for developing better evidence and improving the innovation process?

Up front. Wait for a microphone, if you don't mind. Go ahead.

SPEAKER: Is there any concern that moving to satisfactory benefit and risk ratio will provide less safe and effective drugs? I didn't hear anyone sort of raise that concern and I'm just wondering whether anyone is concerned about that.

MR. McCLELLAN: So maybe John, Rob, maybe start with you all. I think there's sort of agreement that the information, the evidence that we have now on drugs is not perfect. There's no such thing as a safe drug, but I guess you're worried about does this move us in a direction that could be worse on that for patients?

DR. MENDELSOHN: Well, if we take the lung cancer patient that has

metastases, and unless there's a miracle they'll die within four months, they might be willing to take the risk that yes, the drug may -- if we are risk-free they may be protected from a drug which could have caused them harm. But that's a decision that they should be able to make. And I think the point you're making is yes. If we reduce the barriers and say we're going to accept more risk, there will be some failures. And therefore, we shouldn't do that for sleeping pills or for something for diabetes which is a disease that hopefully you live 50 or 60 years with even though you have problems, but for end stage lung cancer, for somebody who is developing Alzheimer's disease and you'd like to not have them go to a nursing home for 10 years which is what happens now, maybe accepting that risk that yes, you might fail more often. It has to be in the right balance of risk versus benefit the way I look at it. A very good question.

MR. McCLELLAN: And a place to start may be some of the higher risk patients.

DR. MENDELSOHN: Right.

MR. McCLELLAN: But FDA does try to take --

DR. MENDELSOHN: Of course.

MR. McCLELLAN: -- on their behalf, they do try to take account of the specific risk-benefit ratios for those patients but for some of these new models may be a good place to start.

MS. BROOKS: Although I would add even in a field like Parkinson's, many of the patients would like -- many scientists believe that drugs that have failed in the past failed because we intervened too late. And so another way to think about this is what risk are we willing to take with earlier stage or at-risk patients? And so while that's probably not the place to start, I think -- I wouldn't be surprised to see that evolution. And again, Alzheimer's provides an interesting precedent to kind of tease out the definition of

mild cognitive impairment from AD which really opens the door for treatment in that indication. And I think -- so in diseases like neurodegeneration, can we look at taking more risks earlier as opposed to no risk at the very early stages?

MR. McCLELLAN: Earl, quick comment?

DR. STEINBERG: Yeah. There's a difference between, you know, whether we know something about how a drug performs and what risk-benefit ratio we're willing to accept. The latter is really a value judgment, and people can vary widely in the risks that they're willing to incur for almost anything. And that's quite -- that doesn't mean that we want to approve things that we don't know at all how they're going to work in a particular situation, but once that evidence is available, the idea that there's a bright line, you know, is really a picture.

DR. AUSTIN: And there are examples where this has happened, of course. I think everybody's favorite example is Tysabri for multiple sclerosis, which when that drug was approved there was a higher rate of rare neurological complication called PML, and that drug was pulled off the market. But because of the urgent request of the MS community, it was put back on the market. It has all kinds of warnings but it allows the MS patient to say, okay, given what my course is and what my likely prognosis is, and the risks of this drug, that allows them to make that decision. And the adverse events have continued to happen at about the same rate. But I think the community seems to be quite happy now with that balance.

MR. McCLELLAN: We have time for maybe one more question. I saw one back here. I don't know who had their hand up first.

SPEAKER: My question is a little bit I think off-track. It's actually the first time I've heard of regulatory science. And I wonder does that apply more generally, like to the financial industry where you hear much more about it? And can you benefit from

any work that they're doing or vice versa?

MR. McCLELLAN: Anyone want to take this outside of health care? I think they feel like they've got a full plate within the health care industry.

Maybe a quick question here?

SPEAKER: I just had a quick question because one of the themes today was better partnerships and academia was mentioned a couple of times. I think Dr. Conley and Dr. Austin, you mentioned one with NIH and eight pharma companies. I missed the name of that initiative. But what do you see or how do you see the role of academia in moving this forward with biomedical innovation? Or what can universities do now to engage and get involved without just waiting on the next RFA?

DR. CONLEY: Well, I mean, one thing I would say is that I'm very happy when I hear about the academic initiatives establishing Centers for Excellence and Partnerships. I think one of the things we'd like to move away from is in industry we often do consultations and sort of one-off partnerships, and it often raises a concern of conflict of interest. And again, it's kind of, as you were mentioning, the catalyst. What we'd very much like to move forward is to be able to bring in our academic colleagues more and more but in neutral space that could answer that conflict of interest in a positive way.

MR. McCLELLAN: And that is the model that Ed was discussing earlier.

DR. CONLEY: It is. That's right.

MR. McCLELLAN: The Partnership for Advancing Therapeutics.

DR. CONLEY: That's right.

MR. McCLELLAN: And we're just getting started with that. Any early returns? Any early views about what's working and what's not there?

DR. AUSTIN: Well, I should just say I think in my view where the innovation is happening now in the space is in academia, I think. And if you listen to what

John was talking about, it's a perfect example of this. And it's for a number of reasons, but if you look at the number of organizations that have gotten interested in this space in the academic domain, it's dramatically bigger than it was 10 years ago. And one of my long-term goals for NCATS is absolutely to have translational science be a bona fide accepted academic discipline which is very robust within academic medical centers and universities, the same way biochemistry is now. I think that's absolutely what we have to have to win this battle over the long term.

MR. McCLELLAN: And there are a number of academic programs as was mentioned earlier that are moving in this direction, new programs moving in this direction.

Well, we certainly didn't solve all these issues with new directions and biomedical innovation today but I think you all did a terrific job of raising issues. And this actually -- because this set of problems is so critical, this seems like a good thing to have you all back in the not too, too distant future to see how we're doing on making progress. I heard lots of room for optimism despite the depth of these challenges.

So I'd like to thank all of our panelists for their contributions today, and also a special thanks to the staff at Brookings who made this event come together, including Greg Daniel, Aaron Rubens, Morgan Romine, Beth Rafferty, Sarah Tratralaton, and Larry Kocot, and also again a special thanks to the Irene Diamond Fund for making this event and a whole bunch of related activities at Brookings possible as we keep trying to make progress on these critical issues of biomedical innovation.

And finally, thanks to all of you for attending. It's been a pleasure to be here with you this afternoon. Thank you.

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