

UNITED STATES OF AMERICA{PRIVATE }  
NATIONAL INSTITUTES OF HEALTH

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SCIENTIFIC MANAGEMENT REVIEW BOARD  
(SMRB)

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TUESDAY  
SEPTEMBER 14, 2010

+ + + + +

The Scientific Management Review  
Board convened in Conference Room 6 of  
Building 31 at the NIH Campus, Bethesda,  
Maryland, Norman Augustine, Chair, presiding.

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SUSAN B. SHURIN, M.D.  
LAWRENCE A. TABAK, D.D.S., Ph.D.  
HAROLD E. VARMUS, M.D.  
A. EUGENE WASHINGTON, M.D.  
HUDA Y. ZOGHBI, M.D.

EX OFFICIO MEMBERS PRESENT:

FRANCIS S. COLLINS, M.D., Ph.D.

DESIGNATED FEDERAL OFFICIAL:

AMY PATTERSON, M.D., Executive Secretary

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ALSO PRESENT:

JOHN I. GALLIN, M.D., Director of NIH  
Clinical Center  
CHARLES BAUM, M.D., Ph.D., Pfizer, Inc.  
JESSE L. GOODMAN, M.D., M.P.H., US FDA  
STEVEN M. ROWE, M.D., M.S.P.H., Cystic  
Fibrosis Foundation  
RAYMOND C. BERGAN, M.D., Northwestern  
University  
ROBERT M. CALIFF, M.D., Duke University  
Medical Center  
GREGORY C. SIMON, J.D., Pfizer, Inc.  
MARY L. DISIS, M.D., F.A.C.P., University  
of Washington  
JAMES H. DOROSHOW, M.D., NIH  
SUSAN OLD, Ph.D., NIH  
THOMAS M. MILLER, Ph.D., M.B.A., NIH  
MICHAEL G. KURILLA, M.D., Ph.D., NIH  
BRIAN K. HALAK, Ph.D., Domain Associates  
THOMAS R. INSEL, M.D., National Institute  
of Mental Health  
WILLIAM D. MATTHEW, Ph.D., National  
Institute of Neurological Disorders  
and Stroke  
JAMES F. JORKASKY, Executive Director,  
National Alliance for Eye and  
Vision Research  
LYRIC JORGENSON, PhD, NIH

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1 P-R-O-C-E-E-D-I-N-G-S

2 8:07 a.m.

3 CHAIR AUGUSTINE: (presiding) Good  
4 morning, everyone. We'll call the meeting to  
5 order.

6 Thank you for the terrific  
7 turnout. The attendance record of this group  
8 has been, I think, better than any group I  
9 have ever served on of this size. We  
10 appreciate that.

11 This is the sixth meeting of the  
12 full SMRB. We don't even keep count of the  
13 number of meetings of our subgroups, but the  
14 number is significant.

15 I would like to welcome  
16 particularly our guests today who are going to  
17 be speaking with us, and also the visitors who  
18 come because of their interest in the topics  
19 that we are going to be addressing.

20 I should probably comment at the  
21 outset that, as is always the case, our  
22 meetings are being telecast to the public. So,

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1 if you would be sure to do what I didn't do,  
2 in other words, turn on your microphone before  
3 you speak? This is a push-to-talk system. So,  
4 when you're done, you will have to push to  
5 turn it off.

6 I'm told that only one of our  
7 members won't be able to join us for at least  
8 most of the meeting. That's Sol Snyder. But  
9 Drs. Powell and Zoghbi and Varmus, and Kelly  
10 and Brody, will be joining us either for all  
11 day tomorrow or the last three will be  
12 arriving here very shortly, I'm told.

13 We have a very full agenda, as you  
14 all have undoubtedly noticed. We are now at  
15 the position -- and we'll come back to this --  
16 where we have complied with the law that has  
17 established this Committee, so that we can  
18 start making some decisions. And as I say,  
19 we'll talk about that a little bit more later  
20 on, or perhaps I should say we should make  
21 some recommendations.

22 Probably the first thing we should

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1 do, for the benefit of our guests, is go  
2 around the table and introduce ourselves.

3 Arthur, perhaps we could start  
4 with you?

5 MEMBER RUBENSTEIN: Sure. Arthur  
6 Rubenstein from the University of  
7 Pennsylvania.

8 MEMBER TABAK: Larry Tabak, Deputy  
9 Director, NIH.

10 MEMBER HODES: Richard Hodes,  
11 National Institute on Aging.

12 MEMBER RODGERS: Griffin Rodgers,  
13 National Institute of Diabetes and Digestive  
14 and Kidney Diseases.

15 MEMBER CASSELL: Gail Cassell, Eli  
16 Lilly.

17 MEMBER WASHINGTON: Eugene  
18 Washington, University of California, Los  
19 Angeles.

20 DIRECTOR COLLINS: Francis Collins,  
21 Director of NIH.

22 And I should have mentioned Larry

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1 Tabak is attending this meeting now as the  
2 Principal Deputy Director of NIH, having  
3 stepped into the role previously held by  
4 Raynard Kington and already very ably taking  
5 on a whole host of important and challenging  
6 tasks.

7 (Applause.)

8 MEMBER KATZ: I'm Steve Katz,  
9 Director of the National Institute of  
10 Arthritis and Musculoskeletal and Skin  
11 Diseases.

12 MEMBER SHURIN: Susan Shurin, the  
13 Acting Director of NHLBI.

14 MEMBER BERG: Jeremy Berg, Director  
15 of the National Institute of General Medical  
16 Sciences.

17 MEMBER BRIGGS: Josie Briggs,  
18 Director of the National Center for  
19 Complementary and Alternative Medicine.

20 MEMBER FAUCI: Tony Fauci, Director  
21 of NIAID.

22 MEMBER GOLDIN: Dan Goldin, the

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2                   MEMBER ROPER: Bill Roper from the  
3           University of North Carolina.

4                   EXECUTIVE SECRETARY PATTERSON: Amy  
5           Patterson, Office of the Director, NIH.

6                   CHAIR AUGUSTINE: And I'm Norm  
7           Augustine. It's my privilege to chair the  
8           SMRB. I use the word "privilege" very  
9           seriously. I think all of us would view that  
10          it's a privilege to serve this great  
11          institution that has accomplished so much, and  
12          hopefully to help it accomplish even more in  
13          the future.

14                   And I, too, should have -- Francis  
15          mentioned Larry's new responsibilities, and we  
16          look forward to working with you in both  
17          roles, as a member of this Committee and your  
18          new role.

19                   Also, I want to point out that --  
20          oh, there's Harold now. He's here. We did this  
21          over the telephone in our last telephone  
22          conference, but it is a particular privilege

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1 to have Harold join this group. There are few  
2 people that know more about this institution  
3 than he.

4 So, welcome, Harold. We're proud  
5 to have you.

6 Again, we have a lot to  
7 accomplish. The meeting kind of breaks into I  
8 guess three parts.

9 The first part, we are going to  
10 talk about the Intramural Research work and  
11 the work of our subgroup or our group that has  
12 been dealing with that. They have focused very  
13 much on an appropriate strategy for it going  
14 into the future in terms of both usage and in  
15 terms of funding. And we will be hearing about  
16 that in just a few moments.

17 We will be voting on the report of  
18 that Committee this morning. As you will hear  
19 later, as with most everything we've dealt  
20 with, there are some complicating factors that  
21 we'll have to address, but we'll deal with  
22 that at the appropriate time.

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1                   Then we will turn to the latest  
2                   task of the SMRB, which is the one on  
3                   translational medicine and therapeutics,  
4                   referred to as the TMAP Working Group. Arthur  
5                   has been kind enough to agree to chair that  
6                   because there is close coupling to the work  
7                   that his committee was already doing. We will  
8                   come to that, then, later in the day.

9                   Tomorrow, after lunch, we will  
10                  turn to the work of the Substance Use, Abuse,  
11                  and Addiction Working Group. And there, too,  
12                  we have a vote to take, which will, of course,  
13                  be very important.

14                 I think everybody has had a chance  
15                 to read the reports of those groups. In my  
16                 view, they were extraordinarily well-written.  
17                 You also come away with the conclusion that  
18                 these are not easy questions. They have done,  
19                 I think, a good job of balancing the various  
20                 perspectives. So, we should be in a very good  
21                 position to vote on that issue tomorrow in  
22                 terms of what we would like to recommend to

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1 Francis and the Congress.

2 Before we proceed, a couple of  
3 administrative announcements. One is to the  
4 members of the public who would like to speak  
5 during the comment period this afternoon.  
6 There is a signup sheet at the registration  
7 table.

8 And if you would sign up, we'll  
9 take people in the order they sign up. There's  
10 obviously a limited amount of time. So, it is  
11 kind of first-come, first-serve. We will ask  
12 each of those who do speak to hold their  
13 comments to five minutes. So, you can be  
14 thinking about that.

15 And obviously we welcome inputs,  
16 written inputs, that are more extensive. We  
17 have a website, and you can find us all here  
18 at NIH with addresses, particularly through  
19 Dr. Patterson's office. And please feel free  
20 to share your views with us.

21 Secondly, the minutes for the  
22 various meetings that have been taking place

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1 are in your package or were sent to you with  
2 your package. And I must say they're one of  
3 the most extensive minutes I've ever seen,  
4 really very well-done.

5 I was reminded of my lawyer  
6 friends who tell me the person who takes the  
7 most notes gets the longest deposition. But  
8 whatever the case, the minutes are extensive,  
9 and we should vote on those.

10 So, would there be a motion?

11 MEMBER FAUCI: So moved.

12 MEMBER CASSELL: Second.

13 CHAIR AUGUSTINE: Thank you very  
14 much.

15 All those in favor?

16 (Chorus of ayes.)

17 Opposed?

18 (No response.)

19 Okay. We have another  
20 administrative item that is very important. It  
21 has to do with our conflict of interest, the  
22 rules that we have to comply with.

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1                   Amy, would you want to brief us on  
2                   that?

3                   EXECUTIVE      SECRETARY      PATTERSON:  
4                   Certainly. Thank you, Norm.

5                   So, as is our protocol, at the  
6                   beginning of each meeting we like to remind  
7                   you about the steps we take and that you take  
8                   and the loads of information that you send us  
9                   to review with an eye toward identifying any  
10                  potential conflicts between your private  
11                  interests and the public interests in your  
12                  capacity of serving on this Committee.

13                  I just would like to remind each  
14                  and every one of you that today you are a  
15                  special, very special, government employee,  
16                  and to be mindful of that as we carry on the  
17                  discussions over the next two days, and be  
18                  mindful of any potential conflicts between  
19                  your private interests and the matters at  
20                  hand.

21                  Thank you.

22                  CHAIR AUGUSTINE: Thank you, Amy.

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1 I would be remiss if, before we go  
2 ahead, I didn't thank the members of the staff  
3 who work behind the scenes to set this meeting  
4 up. The amount of paper that has gone by and  
5 the amount of effort that has gone into it is  
6 remarkable. I hope that those who are not in  
7 this room could be thanked by those who are in  
8 the room on our behalf for all they have done  
9 to prepare for this meeting.

10 And before we launch into the  
11 subject matter, Francis, I would like to give  
12 you the first word, if you have anything you  
13 would like to say at this point.

14 DIRECTOR COLLINS: Thanks, Norm.

15 Very briefly, just to thank all of  
16 you for the hard work that's gone into getting  
17 us to this point and to underline what you  
18 have said about the importance of this  
19 particular meeting because of arriving at the  
20 point of taking votes and making  
21 recommendations about two major areas: the  
22 Clinical Center at NIH and the debates about

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1           what to do with regard to two institutes, the  
2           Alcohol Institute and the Drug Abuse  
3           Institute, in terms of going forward in  
4           research on substance use, abuse, and  
5           addiction.

6                       So, this is the culmination of a  
7           lot of hard work and deliberations. And I want  
8           to thank you and the groups that have done so,  
9           particularly the Chairs who have led that  
10          effort. And we will be hearing from them  
11          during the course of today and tomorrow.

12                      So, Arthur Rubenstein, especially  
13          thank you for your hard work on the first of  
14          those, and Bill Roper on the second.

15                      And also, to say that we are going  
16          to spend a big chunk of the meeting looking at  
17          this next question of whether there are  
18          opportunities to further improve the  
19          efficiency and the scientific innovative  
20          potential for translation in this new group  
21          that Arthur has agreed once again to lead -  
22          and thanks to him - the TMAP group.

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1                   And I'm going to be very  
2 interested to hear the substance of those  
3 discussions, because I think we have a real  
4 opportunity here, but it's one that needs to  
5 be addressed thoughtfully.

6                   So, I think I would also want to  
7 echo what Norm said at the beginning about my  
8 degree of being impressed by the faithful  
9 service of all of you who have been involved  
10 in this from the beginning. This is a group of  
11 very busy people who could easily come up with  
12 excuses to be somewhere else, and yet you have  
13 faithfully attended these meetings and really  
14 put your own best ideas and thoughtfulness  
15 into this process. That's been enormously  
16 appreciated.

17                  I found this to be an extremely  
18 valuable group for these kinds of  
19 considerations. So, thank you, and I look  
20 forward to a really interesting couple of  
21 days.

22                  CHAIR AUGUSTINE: Well, thank you,

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1 and, Francis, we understand that there are  
2 some hearings on the Hill on stem cell  
3 research this week. So, if you step out, we  
4 will fully understand.

5 DIRECTOR COLLINS: I will,  
6 unfortunately, tomorrow morning have to be  
7 involved in preparing for this Thursday's  
8 hearing in front of Senator Harkin about stem  
9 cells and the latest earthquakes that have  
10 happened in terms of federal oversight.

11 CHAIR AUGUSTINE: With that, we can  
12 delve into the thrust of the meeting, the  
13 first item, of course, being the work of the  
14 Intramural Research Group, which Arthur has  
15 been chairing.

16 So, could we turn to you?

17 MEMBER RUBENSTEIN: Yes.

18 Good morning, everyone, and  
19 thanks, Norm.

20 I would like to begin by thanking  
21 the members of our group for their hard work  
22 and perseverance. We had a terrific group. We

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1 have worked very well together.

2 I also want to just thank Amy  
3 personally and the staff who worked with her,  
4 her colleagues. I couldn't think of a better  
5 group to deal with challenging and important  
6 problems.

7 To remind you, the charge to the  
8 Intramural Research Program Working Group has  
9 been to look at the Intramural Research  
10 Program and determine the changes in its  
11 organization and/or management function.

12 In terms of this, I hope that you  
13 all have had a chance to read the written  
14 report. This is going to give you a high-level  
15 summary of it. But I think the report itself,  
16 which we collectively did with a lot of staff  
17 support, really does spell out in very clear  
18 ways what the issues are and what some of the  
19 challenges and conclusions are.

20 So, this high-level summary I hope  
21 will just paint the picture, but the report  
22 itself, if you have had a chance to read it,

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1 does indicate our deliberations and the pros  
2 and cons of the decisions we have made.

3 Given that the recent internal  
4 assessments have indicated an urgent need to  
5 address the fiscal vitality of the NIH  
6 Clinical Center, our group agreed to first  
7 focus its efforts on providing an analysis of  
8 and recommendations regarding the fiscal  
9 sustainability and utilization of the NIH  
10 Clinical Center.

11 We have a broad mandate to look at  
12 the Intramural Research Program, but  
13 realistically speaking, because of a whole  
14 variety of governance, vision, and budget  
15 issues, with the agreement of the overall  
16 committee, we decided to look at this first.

17 This is our group. I won't go  
18 through the names. You know them well. But I  
19 do want to just compliment them and thank you.  
20 We have worked very, very well as a group, and  
21 when there were divergent opinions, which  
22 there certainly were, we worked hard to come

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1 to a consensus and be supportive of each  
2 other's points of views.

3 While our group has thought about  
4 this issue and regularly updated the SMRB  
5 regarding its process, I would like briefly to  
6 remind you of the steps that we have  
7 undertaken since April last year to try to see  
8 that we were informed by a wide variety of  
9 opinions and took into consideration  
10 alternative points of view about what might we  
11 do.

12 Our group has held eight  
13 teleconferences and three in-person meetings,  
14 and most recently, in May this year, we had a  
15 stakeholders' consultation. We heard opinions  
16 from informed people from all around the  
17 country as well as intramurally at the NIH.

18 And as you may recall, we have  
19 also had input from a whole variety of  
20 important people which are listed here:  
21 hospital administrators, external potential  
22 users of the Clinical Center. This is a really

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1 important thing, because it is a challenging  
2 issue, and the question was the feasibility  
3 and how one would get this done in a practical  
4 sense.

5 The Advisory Board for Clinical  
6 Research, investigators within the Intramural  
7 Program, and the directors of the NIH, as well  
8 as the public. So, we have been open to all  
9 variety of opinions, thinking about how we  
10 might proceed with this.

11 Now I would like to briefly go  
12 through the findings with you.

13 Of course, the most important  
14 thing is to acknowledge the important strength  
15 of the Clinical Research Center here. I will  
16 not in detail today talk about all the details  
17 about why this is such an important center in  
18 the NIH as well as the country and all its  
19 great accomplishments and the important things  
20 that have made it so successful.

21 Here are some of them, though,  
22 just briefly, to remind you:

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1                   Investigators can put their full  
2                   attention to research without much worry about  
3                   budgets, although despite saying that, the  
4                   budget issues have crept in. In a way, that  
5                   has been the incentive for this report.

6                   People can respond briefly and  
7                   nimble to new challenges, perhaps more so here  
8                   than at other places.

9                   Patient care is fully funded, and  
10                  this is, of course, a huge advantage for  
11                  patients and their family with problems who  
12                  come here from around the country.

13                  The staff has access to cutting-  
14                  edge technology. And those of us who toured  
15                  the Clinical Center were impressed by the up-  
16                  to-date technologies and opportunities to do  
17                  clinical research at the highest level.

18                  And the opportunity to conduct  
19                  high-risk trials for life-threatening  
20                  diseases, sometimes which are very expensive  
21                  but have very broad implications when some of  
22                  the answers are discerned from beautiful

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1 investigations.

2 And of course, sometimes we don't  
3 succeed. That's acceptable, too, if one's  
4 doing high-risk research. That seems more  
5 possible to do here often than at other  
6 places.

7 And here's a few more: critical  
8 mass of highly-skilled individuals. When we  
9 listened to the testimony given by many of the  
10 investigators who were passionately involved  
11 in studying and looking after patients here,  
12 it was extraordinarily impressive, some of the  
13 advances and reasons that they have made new  
14 discoveries.

15 Many are a critical role in first-  
16 in-human studies and rare disease research,  
17 which may not be able to be done, except very  
18 expensively, elsewhere.

19 It supports longitudinal studies.  
20 Of course, we study human biology based in  
21 basic science, which is, of course, such a  
22 beautiful thing when it works well.

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1                   And of course, there are important  
2                   training opportunities which have always been  
3                   a hallmark of both the Center and, of course,  
4                   the NIH mission.

5                   So, there are many reasons to  
6                   think about the Clinical Center as a  
7                   critically important jewel in the NIH, but  
8                   also nationally, particularly at a time when  
9                   there is a national view that moving  
10                  discoveries from patients into a broader thing  
11                  of more help for individuals around the  
12                  country is important.

13                  With that, now I would like to  
14                  move through some quick review of our findings  
15                  and recommendations. And it's important that,  
16                  in a sense, this is a summary of what's in the  
17                  report, because I'm going to give a very high-  
18                  level summary. Of course, if there are  
19                  questions, I or my colleagues here would be  
20                  happy to answer them.

21                  When we looked at the challenges,  
22                  really we were able to break them down into

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1 three themes. Having identified this has given  
2 us a framework to think about our report in a  
3 very specific and, I would say, focused way.

4 We looked at the vision and role  
5 of the Clinical Center, its governance, and  
6 the budget. They all intersect, of course, and  
7 impact on each other. Trying to move forward  
8 with each of them needed some reassessment of  
9 the other one, and we have tried to do that in  
10 a cohesive way.

11 In terms of the vision and role,  
12 the challenge here was really whether there  
13 was an opportunity to broaden the scope of the  
14 patients and investigators who are involved in  
15 the Clinical Center. And some of the reasons  
16 that this seemed to be worthwhile looking at  
17 in a serious way was some of the barriers and  
18 problems that investigators believed were  
19 extant in the Clinical Center at the moment.

20 So, there was a perceived lack of  
21 prioritization and commitment to clinical  
22 research because of some difficulties -

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1           administratively, and particularly budgetwise  
2           - of doing it at this time, at a time it was  
3           so important from a point of view of the  
4           important mission in the country, as this is.

5                       There       were       barriers       to  
6           partnership, particularly between intramural  
7           and extramural collaborations and intellectual  
8           property issues. This is an understandable but  
9           difficult problem, and we thought it was  
10          really important to think about whether we  
11          could make that more streamlined and  
12          straightforward.

13                      And there are also barriers to  
14          recruitment and retention of investigators  
15          because of a variety of salary and budget  
16          issues that are now in the purview of the  
17          government, particularly with no draft  
18          anymore, and so forth.

19                      So, there were real issues that  
20          didn't say the Clinical Center wasn't doing  
21          well, but they were challenges as to whether  
22          it was an opportunity for it to do new and

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1 important things in a different way.

2 In terms of the governance, some  
3 of the challenges were a lack of trans-NIH  
4 vision for priority-setting in the clinical  
5 research. This was particularly made worse by  
6 some of the budget issues which were quite  
7 understandable, but involved institutes  
8 disproportionately in a sense. And there were  
9 also complexities in the administrative  
10 approval process, which had grown up over time  
11 and probably, when looked at in a new way,  
12 gave opportunities for making it more  
13 straightforward and streamlined.

14 Here you can see the current  
15 organization of the oversight structure. I  
16 won't go through it in detail.

17 There were good reasons for all of  
18 these committees, subcommittees, and oversight  
19 bodies. They are spelled out in some detail in  
20 the report, but it did make many levels of  
21 oversight and perhaps delayed decision-making  
22 and made it more complex than it should be.

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1                   So, this was an opportunity to  
2                   think about it as we streamlined and thought  
3                   about new administrative and fiscal structures  
4                   to simplify the governing structure. I think  
5                   we have come up with a scheme that maintains  
6                   the best of all these operations, but does it  
7                   make it simpler and more streamlined?

8                   And of course, a big driving force  
9                   for all this was the projections of budgets in  
10                  the next several years which were really  
11                  difficult to think about in a constructive  
12                  way, to both support and enhance and believe  
13                  in clinical research and the utilization of  
14                  the Clinical Center, but also find ways to  
15                  fund it in a way that was supportive of the  
16                  leadership within the NIH in a way that would  
17                  be necessary to utilize the Center at its  
18                  maximum.

19                 So, all of these things, then, as  
20                 you can see, were reasonable challenges for  
21                 our Working Group to look at, particularly in  
22                 terms of the budget. There were increasing

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1 costs of the Clinical Center, which are now  
2 paid for proportionately by the intramural  
3 institutes, the institutes in general, which  
4 does not keep up with inflation.

5 The current structure is called  
6 school tax, and there's a tax on each of the  
7 institutes to pay for the Clinical Center. The  
8 cost shifts have had unintended and  
9 undesirable consequences, tending to reduce  
10 the interest and enthusiasm to use the  
11 Clinical Center by investigators in each of  
12 the institutes because of budget issues that  
13 impacted on the opportunity to do research and  
14 always had to be considered. Now that's not  
15 unusual, but some of the budget issues were  
16 disproportionately onerous on various  
17 institutes.

18 And the budget mechanism didn't  
19 really have an easy way, although it was  
20 possible with very great difficulty to support  
21 the involvement of investigators outside the  
22 NIH institute either collaborating or using

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1 the Clinical Center in a straightforward way  
2 for other opportunities.

3 So, these were important barriers  
4 to streamlining and using the Clinical Center  
5 which we thought were worthy of review.

6 So, these are some of the issues  
7 that we dealt with. In a sense, we have come  
8 up with some straightforward -- I think, of  
9 course, they're always complicated to put them  
10 into practice -- but recommendations which we,  
11 as the Work Group, believe should move the  
12 Clinical Center forward within the NIH  
13 intramural community, and which we hope will  
14 maintain, of course, all the good parts  
15 without damaging them and produce new  
16 opportunities that should be, I think,  
17 advantageous.

18 So, we would like to suggest that  
19 we position the Clinical Center more as a  
20 national resource than just a resource within  
21 the NIH, which it should remain, of course. We  
22 hope that there will be opportunities to

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1 prioritize clinical research both within and  
2 outside the NIH by a new mechanism of both  
3 governance and budgets.

4 The budget changes we hope will  
5 ensure fiscal sustainability and a stable and  
6 responsible budget without having significant  
7 impact on other areas of the NIH intramural  
8 community, as I'll describe when I talk about  
9 our recommendations.

10 And also, as Francis has put  
11 forward, the idea of the TMAP, that the  
12 Clinical Research Center, of course, should be  
13 a central focus and opportunity, together with  
14 other opportunities, like CTSA's and so forth,  
15 to take advantage of this new effort both at  
16 the NIH and across the country.

17 So this will, then, change the  
18 vision, governance, and budget, but in a way,  
19 again I stress, that maintains the best of  
20 what we have and moves the opportunities  
21 forward in each of these areas.

22 So, I'll stop there for a moment

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1 and just see whether there are any questions  
2 about the setup and framework and terms, and  
3 then I'll go to the recommendations.

4 Any thoughts?

5 (No response.)

6 All right. So then this is what we  
7 have come up with which our Working Group  
8 would like to present to the full SMRB today.

9 So, first of all, we would like to  
10 advise that the committee will recommend that  
11 the Clinical Center has the potential to serve  
12 as a national resource for clinical research.  
13 It has state-of-the-art facilities and  
14 resources, and of course, we, therefore,  
15 believe it could serve the needs of both  
16 internal and external investigators and play a  
17 more significant role in supporting and making  
18 possible leading-edge clinical research and  
19 therapeutic development across the country.

20 Again, this will not be a simple  
21 thing to do, but we believe we could put in  
22 place a variety of rules and regulations that

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1 would make it more straightforward than it is  
2 now.

3 We recommend an expanded vision  
4 and role for the Clinical Center in this  
5 regard and position it to truly function as a  
6 national resource. There are tremendous  
7 infrastructure resources, technology, and  
8 opportunities there for drug development that  
9 we do believe could really enhance  
10 investigators both intramurally and across the  
11 country.

12 Here are just some of them. Many  
13 of them are listed in the report. But when one  
14 asks, what are the key attributes and  
15 particular advantages of the Clinical Center,  
16 and when one goes on a tour, one is very  
17 struck by them. Here are some of the things  
18 that most places around the country don't have  
19 or do not have in the scope and expertise and  
20 excellence that are present here in the  
21 Clinical Center.

22 I won't go through them all, but I

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1 would say many investigators around the  
2 country would have big thoughts about the  
3 possibility of collaborating or potentially  
4 personally using some of these resources,  
5 which are quite extraordinary.

6 And I think it is also true to say  
7 that some of them are underutilized. They are  
8 very expensive infrastructure facilities, and  
9 they are utilized but sometimes not at the  
10 level at which they are capable of being used.

11 So, this is the attractiveness of  
12 recommending the opportunity to expand the use  
13 of the Clinical Center, both to intramural and  
14 extramural investigators.

15 The second point we would like to  
16 recommend is a more streamlined governance  
17 structure that facilitates the development of  
18 a clear, coherent plan for the Clinical  
19 Research Center, and where the decisions made  
20 and the oversight is straightforward, answers  
21 to the Director, and makes recommendations  
22 without it being overseen by layers and layers

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1 of a variety of committees and bureaucracy  
2 that really we felt did not add particularly  
3 to the enhancement of the Center's  
4 performance.

5 This is the simplified structure.  
6 The exact composition and makeup of each of  
7 these committees is detailed in your report.  
8 But, basically, there is significant input, of  
9 course, from the Intramural directors of the  
10 institutes. You can see that on the left. We  
11 would maintain the Advisory Board, the ABCR,  
12 but look to it with a variety of subcommittees  
13 that would have input into it, and they would  
14 answer directly to the director.

15 It is not a fundamental change.  
16 It's a simplification change and streamlining  
17 and getting rid of the layers of oversight  
18 that, I think, both intramurally and  
19 extramurally we felt did not add a lot of  
20 value to the oversight and governing structure  
21 of the clinical setting.

22 And equally and also very

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1 important was the issue about the budget. When  
2 the projections were made of how the Clinical  
3 Center would be funded over the next five to  
4 ten years, it utilized a significant increase  
5 of money from the intramural budget, and this  
6 led to the disadvantages that I described to  
7 you earlier.

8 And so what we really wanted to do  
9 was find a stable, responsive budget  
10 transformed by a rational process of planning  
11 and priority-setting and linked to a strong  
12 planning process that would be transparent and  
13 straightforward and not lead to unintended  
14 consequences when new opportunities existed in  
15 terms of clinical research.

16 So, we have discussed a whole  
17 variety of options and spent a lot of time  
18 with this because, of course, when one starts  
19 changing budget allocations, there's always  
20 some people who will legitimately feel worried  
21 about what the impact is on a variety of other  
22 budgeting. Pretty much, the total budget is

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1           unlikely to go up; otherwise, we wouldn't be  
2           having this kind of challenge.

3                   And so we have thought very  
4           carefully about the impact of such changes,  
5           and, I think, with a lot of deliberation and  
6           input, we feel comfortable about the kind of  
7           recommendation that we are going to make.

8                   So, we discussed a spectrum of  
9           options, analyzing in great detail the  
10          strengths and weaknesses of five particular  
11          options. These analyses are found in Appendix  
12          D of the report. And I do hope that you have  
13          either read that or will look at it, because,  
14          in a sense, the pros and cons of each of these  
15          -- of course, none of them are just obviously  
16          the best -- did consume a lot of our  
17          deliberations. And we feel quite strongly that  
18          the issues that we've come up with are  
19          worthwhile, based on that kind of analysis.

20                   The options discussed, of course,  
21          these five, were to keep the status quo. That  
22          is the current school tax of the tax on each

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1 of the institutes.

2 A second option explored was a  
3 modified version of the status quo. And this,  
4 not to snow you with details, deals with  
5 issues of fixed and variable costs which could  
6 be dissociated and which we thought about a  
7 lot but in the end did not seem to make a  
8 significant, overall, long-term advance in  
9 terms of what we wanted to accomplish.

10 The third and fourth and fifth  
11 options are all some version of a line-item  
12 approach to Clinical Center budgeting. This  
13 approach would result in funds for the  
14 Clinical Center to be derived from the overall  
15 NIH budget and not just from the NIH  
16 Intramural Research Program. I want to stress  
17 that is the key policy change that, if this is  
18 adopted by the full SMRB, would be the issue.

19 At the moment, the Clinical Center  
20 is funded from the Intramural Research  
21 Program, and we believe now it should be a  
22 mixture of both the Intramural Program and the

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1 total NIH budget -- of course, of which the  
2 Intramural Program is a key part.

3 The third option would include the  
4 Center as a line item in the budget of the  
5 institutes and centers. You can see that "Fee-  
6 for-Service for Variable Costs" -- that line  
7 item on the IC budget.

8 The fourth would be a budget in  
9 the Office of the NIH Director, of course, who  
10 has jurisdiction over the whole NIH budget.

11 And the fifth and final option  
12 would be a direct congressional appropriation  
13 for the Clinical Center; the possibility way  
14 over on the right side of this slide.

15 Now you will see a detail --  
16 there's also a table in the Appendix which  
17 talks about the impact of the move of the  
18 Clinical Center to be funded by the whole NIH  
19 budget. Of course, the majority of the funding  
20 would still come from the Intramural Research  
21 Program, but there would be opportunities to  
22 add funds from the total NIH budget in the

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1 Office of the Director. And that's the key  
2 recommendation change that we are making.

3 Analyses and discussions have led  
4 us to recommend this fourth option, the one  
5 circled there, as the preferred funding model.  
6 They all have pros and cons, but in many, many  
7 ways this seemed to be the most advantageous  
8 one, and with little downside in terms of the  
9 amount of money that is moved in terms of the  
10 new suggestion.

11 The consensus view of the Working  
12 Group is that the option meets the criteria  
13 that we set and laid out in terms of what we  
14 wanted to achieve by this reformatting of the  
15 Clinical Center mission.

16 It would facilitate use of the  
17 Center by external investigators, provide  
18 higher visibility for the Clinical Center and  
19 its availability for enhanced clinical  
20 research, both from intramural and extramural  
21 investigators, and also put a high priority on  
22 clinical research at a time that nationally

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1           this is assuming great importance.

2                       And it will enhance the stability  
3           of the Clinical Center, because the funds  
4           would come from a greater pool -- the whole  
5           NIH budget -- although I want to stress again,  
6           the majority of the funds would still come  
7           from the Intramural Research Program, as was  
8           spelled out in the report in great detail.

9                       And this, then, would give some  
10          stability going forward and not lead to  
11          unintended consequences of discouraging  
12          clinical research because of small but very  
13          real budget issues that couldn't be  
14          accommodated easily.

15                      So, that is a summary of what we  
16          have put into the report. I think the report  
17          does spell it out in great detail, and I think  
18          I want to thank again the members, the report,  
19          and the staff.

20                      You will hear from Norm, and I  
21          just put that forward, that this will have to  
22          be thought about in relation to the TMAT

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1 opportunity as well. But I think our Working  
2 Group felt very strongly that this report  
3 dealt with many of the challenges that we had,  
4 and we hope that the committee, the full SMRB,  
5 would at least evaluate it carefully on that  
6 regard.

7 So, thank you, Norm.

8 CHAIR AUGUSTINE: Arthur, thank  
9 you very much and your committee as well.

10 The floor is open to the members  
11 who might want to comment.

12 Harold?

13 MEMBER VARMUS: Well, Arthur, thank  
14 you very much for what's gone into this report  
15 and to endorse the conclusions.

16 But I would like to hear a little  
17 bit more about your first recommendation. I  
18 have been a strong proponent myself of greater  
19 use of the Clinical Center by the extramural  
20 scientific community. It was one of the key  
21 elements in the Nathan report on clinical  
22 research 15 or 13 years ago.

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1                   MEMBER RUBENSTEIN: Right.

2                   MEMBER VARMUS: And yet, it has  
3                   always seemed that there's a pretty  
4                   substantial reluctance of extramural clinical  
5                   investigators to use the Clinical Center.  
6                   There are some exceptions, the Pediatric GIST  
7                   Consortium and a couple of other examples of  
8                   people who came to the NIH from the extramural  
9                   community and worked here on a temporary  
10                  basis.

11                  But, in general, for a variety of  
12                  reasons having to do with distance, the need  
13                  to hold onto one's own patients, the  
14                  reluctance to collaborate with the Intramural  
15                  Program, and cost considerations, there hasn't  
16                  been tremendous use of the Clinical Center by  
17                  the extramural clinical research community.

18                  So, I would be curious to know  
19                  what impediments to that use your group  
20                  identified, what you see as ways to make  
21                  Recommendation 1, which is perfectly, you  
22                  know, it's kosher, but is it actually going to

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1 be followed in reality?

2 MEMBER RUBENSTEIN: That's a key  
3 question we wrestled with a lot of the time.  
4 Of course, there are a lot of bureaucratic,  
5 financial, intellectual property issues that  
6 stand in the way, as you correctly say, and  
7 then there are people who have promulgated  
8 this view, as you correctly point out.

9 So, rather than me answer all of  
10 them, I would ask some of the people on our  
11 Work Group to weigh-in.

12 We have talked to a lot of  
13 extramural investigators. Of course, a lot of  
14 the issues that some of them brought up was we  
15 didn't know these things were available, like  
16 the drug development opportunities, the people  
17 who are looking at musculoskeletal  
18 involvement, and so on. And if they knew more  
19 about what the opportunities were, they would  
20 certainly be interested.

21 And then, of course, the issue was  
22 whether legally, budgetary-wise, and

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1 collaborative-wise, we could make this so that  
2 it wasn't a huge barrier for people who would  
3 just throw up their arms and say, "We'd like  
4 to do it, but we can't. You know, there are no  
5 ways to get around all those bureaucratic  
6 things."

7 So, part of the challenge we had,  
8 which is not solved yet in our Work Group  
9 report, is if this is adopted, for Francis and  
10 his colleagues within the NIH to come up with  
11 a set of rules and regulations that would  
12 streamline the opportunity for extramural  
13 investigators to use it and then for us to  
14 publicize the opportunities available.

15 Perhaps one last comment I'll  
16 make, the issue of translational research has  
17 become so important and so visible around the  
18 country. And perhaps the development of the  
19 CTSA's and their restrictive funding has also  
20 led people to look for added opportunities for  
21 them to do their mission, that maybe the  
22 climate is just different in terms of people's

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1 interest.

2 But it will be a challenge, as you  
3 point out, and we would have to work hard to  
4 make this a reality.

5 Tony, maybe you would comment?

6 MEMBER FAUCI: Yes, just to make a  
7 comment that relates to Harold's question and  
8 Arthur's answer, that we really need to make  
9 sure when people want to understand how this  
10 will work, that they look carefully at Table  
11 1. Because when you're talking about what  
12 contribution from the broad NIH budget this  
13 will be, you said it's a combination of both  
14 with a majority -- it isn't the majority; it's  
15 a fraction of a fraction of a percent of the  
16 total budget.

17 So, the NIH Clinical Center budget  
18 will still be essentially funded by that one-  
19 time transfer of the cost to Building 1, where  
20 it will reside as an OD line item. There will  
21 either be no additional tapping out of the  
22 broad NIH budget if the increase for the NIH

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1 is equal to or more than the increase for the  
2 cost of running the Clinical Center. Only when  
3 the increase of the cost of running the  
4 Clinical Center is greater than the increase  
5 that comes to the NIH as a whole will any  
6 money come out of a pot that's extramural. And  
7 that's very, very clearly delineated in Table  
8 1.

9 And the reason why it relates in  
10 part to Harold's question and to Arthur's  
11 answer is that, yes, we need to make it more  
12 clear what the pathways are -- and that has  
13 not been clear in the past -- of how you can  
14 come in and utilize the Clinical Center.

15 But it's also not going to be  
16 completely free to just come in and say I want  
17 to occupy 10 beds. It won't be that way. We  
18 have to be pretty clear upfront that we'll  
19 have to work out a mechanism whereby there's  
20 money that is used from their own resources to  
21 use what the opportunities are at the Clinical  
22 Center.

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1                   So, that's what makes it a little  
2 bit confusing -- not confusing; it needs to be  
3 more clearly delineated of what those  
4 opportunities are.

5                   MEMBER VARMUS: Can I just follow  
6 up on that?

7                   MEMBER RUBENSTEIN: Please.

8                   MEMBER VARMUS: I haven't seen  
9 enough of the numbers. I did appreciate Table  
10 1. I could see that would have minimal impact.

11                  But for the individual  
12 investigator on the outside, if you consider  
13 someone who's got a CTSA at their institution,  
14 and consider the possibility of having, say,  
15 five or so patients from that extramural site  
16 come to the NIH, what is the approximate cost  
17 to the investigator? Is cost going to be an  
18 impediment to coming?

19                  MEMBER FAUCI: No.

20                  MEMBER VARMUS: You think not?

21                  MEMBER FAUCI: No, it won't. I  
22 mean, if you just want to bring a patient in,

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1 John Gallin has discussed this in the past.  
2 There almost certainly would have to be some  
3 small amount of designation for beds for  
4 people, which would be part of the big  
5 package, not that you have to pay for it.

6 So, it's conceivable, Harold, that  
7 someone could come in, bring some patients in,  
8 and it comes out of the pure running of the  
9 Clinical Center. It's only when they want to  
10 come in with something that goes above and  
11 beyond what the Clinical Center has available  
12 will they be tapped for it.

13 MEMBER RUBENSTEIN: There is an  
14 analysis, Harold, about the underutilization  
15 of the potential of the Clinical Center in  
16 terms of bed utilization, which would not  
17 particularly increase the infrastructure cost.  
18 If the occupancy went up, someone has to staff  
19 it at a certain ratio.

20 So, each of these things, just  
21 like you're asking, would have to be analyzed  
22 in some detail. And this report just gives the

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1 opportunity to do that without going through  
2 each one in detail.

3 Steve?

4 MEMBER KATZ: So, also, in answer  
5 to Harold's point, there has always been this  
6 barrier of intramural/extramural dollars. I  
7 think that we have worked it out with the  
8 lawyers that, prospectively, if someone is  
9 going to utilize a fair amount of resources,  
10 they can designate upfront that they need a  
11 certain amount of money that's going to go for  
12 paying for this over and above the occasional  
13 patient, and it's five or ten patients, a  
14 substantial study that is utilizing a lot of  
15 resources that's going to increase the budget,  
16 that budget will now be allowed.

17 And I think for a long time there  
18 was this barrier that we had in our heads, and  
19 it was really in our heads more so than in  
20 reality, according to the law, that you  
21 couldn't use any extramural money for  
22 intramural purposes. But I think now we've

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1           gotten beyond that.

2                       MEMBER RUBENSTEIN: Just if I could  
3           comment, I just want to add to what Harold  
4           said. This is not saying anything particularly  
5           new. Many of these things are actually  
6           utilized at the moment by a small number of  
7           investigators, usually in partnership with  
8           colleagues at the NIH, and so forth.

9                       And you can see many of them are  
10          really cutting-edge issues that investigators  
11          around the country, if they had some  
12          straightforward way of accessing them, and  
13          particularly at this time, would be very  
14          interested in doing, and we heard from  
15          extramural investigators.

16                      So, of course, the devil's in the  
17          details. How would we streamline a way that  
18          could make it work without people throwing up  
19          their hands and saying, "It's just not worth  
20          it."?

21                      CHAIR AUGUSTINE: Gail?

22                      MEMBER CASSELL: Yes, Arthur, as

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1           you were presenting, I can't recall if in our  
2           committee deliberations that we discussed the  
3           potential of extramural scientists being able  
4           to access the GMP facility. The GMP facility  
5           is state-of-the-art. This is a resource that  
6           is often, most often, not available at the  
7           academic health centers.

8                     And I just wonder...there might be  
9           a demand, even greater demand, for access to  
10          the GMP facility, but with no interest in  
11          enrolling patients in the Clinical Center. Is  
12          that possible?

13                    MEMBER RUBENSTEIN: Yes, we did  
14          talk about that. Of course, when we toured the  
15          facility, which is beautiful and large and  
16          new, that opportunity was pretty clear, that  
17          others may not have that opportunity outside  
18          the NIH. You know, the opportunity to use that  
19          in collaboration seemed to be very real.

20                    Would you like to comment?

21                    DIRECTOR GALLIN: Thank you.

22                    First, I would just like to

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1 elaborate on the answer to Harold's question  
2 and Dr. Fauci's answer about how much would it  
3 cost.

4 We modeled this and came up with  
5 the idea that only the variable costs for  
6 bringing in an additional patient, for  
7 example, would be charged. And we estimated  
8 that would be about 15 percent of a patient-  
9 day's cost, and it would relate to added  
10 nursing cost and some drug costs and maybe a  
11 few other supply costs. But the essential  
12 resources of the hospital would essentially be  
13 available for use. So that's what we came up  
14 with, but there are other models that could be  
15 used.

16 In terms of the GMP facility,  
17 which is something we're very excited about --  
18 and there are a number of other kinds of  
19 resources that could be accessed that would  
20 not relate necessarily to using the facility  
21 for a patient, but to some service that would  
22 enable research somewhere else -- that could

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1 be done, but somehow we would have to come up  
2 with a mechanism to cover the cost; the added  
3 cost, for example, for formulating a new  
4 product to go into a patient.

5 The transfer of the dollars right  
6 now is a barrier. An investigator has come to  
7 me, for example, numerous have come and said,  
8 "Gee, I would like you to do this. Can I pay  
9 for it?" The answer is today, from an existing  
10 grant, it's not possible for us to receive or  
11 keep the funds to cover just the cost for  
12 delivering the service. That needs to be  
13 fixed.

14 MEMBER KATZ: But for a new grant,  
15 it is possible.

16 CHAIR AUGUSTINE: Harold?

17 MEMBER VARMUS: I would just like  
18 to make one brief comment. I don't think we  
19 should overfocus on the finances. I mean  
20 they're important, but there are a lot of  
21 other perceptual issues about working with the  
22 Intramural Program: moving your patients into

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1 a domain where you may lose control; some  
2 sense that an institution depends on the  
3 Clinical Center; the institution itself  
4 doesn't get credit for the work that is done;  
5 the intellectual property issues that you  
6 raised.

7 I think all these other  
8 considerations are extremely important, and I  
9 think some work needs to be done. I strongly  
10 applaud the idea of moving in this direction,  
11 but I think we have to be very sensitive to  
12 the perceptual issues as well as the financial  
13 ones.

14 MEMBER FAUCI: Yes, that is a very  
15 good point, Harold, and we discussed this  
16 during some of our deliberations.

17 One of the points that you make is  
18 clear, and it's unfortunately a misperception,  
19 and maybe an understandable misperception. If  
20 a group comes up in -- and we just modeled a  
21 couple of examples, and you could spend a day  
22 going through all of them.

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1                   For example, by definition, just  
2                   because you bring a patient into a Clinical  
3                   Center, that doesn't mean that (a) you  
4                   necessarily need to collaborate with anybody,  
5                   and you certainly don't have to give up  
6                   control of the patient or essentially  
7                   responsibility for the results that come out  
8                   from that patient.

9                   There will be instances where you  
10                  might want to come in and study a group of  
11                  patients that are already being studied there.  
12                  That, by definition, will be a collaboration.  
13                  But just because you study patients at the  
14                  Clinical Center doesn't mean that you give up  
15                  your patients at all.

16                 MEMBER VARMUS: I think it's  
17                 important not just to write this stuff down,  
18                 but Francis has been considering hiring  
19                 someone to serve as an ambassador to the  
20                 extramural community. This would be a very  
21                 important role for someone who is carrying the  
22                 NIH message out to the grantee institutions.

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1 CHAIR AUGUSTINE: Gail?

2 MEMBER CASSELL: Yes, Harold, I  
3 totally agree with you. I think the perception  
4 of there being a long queue, too, is something  
5 that has perhaps precluded others from trying  
6 to access it in the past.

7 But, as I have said from the  
8 outset, I think the Clinical Center is an  
9 undervalued, underappreciated national and  
10 international resource.

11 I just had the opportunity this  
12 spring to bring in some international groups  
13 from Russia and Taiwan, and they are just  
14 blown away by the Clinical Center, the fact  
15 that you have GMP right there.

16 I just think we need to do a much  
17 better job, all of us, in advertising this  
18 national and international resource, much like  
19 the Rocky Mountain Laboratory in Hamilton,  
20 which, Norm, we hope that you will visit,  
21 because it really is very impressive and  
22 certainly a resource.

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1                   MEMBER VARMUS: Are there any  
2 special restrictions on bringing international  
3 patients to the Clinical Center? I've never  
4 asked that question. I don't think so, but --

5                   MEMBER KATZ: No.

6                   MEMBER VARMUS: Visa problems?

7                   MEMBER RUBENSTEIN: Unfortunately,  
8 we had enough challenges, but it's an  
9 interesting thought.

10                  CHAIR AUGUSTINE: Are there other  
11 questions or comments from the group?

12                  (No response.)

13                  I think, as usual, Harold, you put  
14 your finger on the problem or the challenge --  
15 not a problem, but the challenge. Part of this  
16 is going to be how well we implement.

17                  I have had in the back of my mind  
18 as I have listened to this debate for the past  
19 few months, and I may have even mentioned this  
20 before, a quote from Shakespeare where -- I  
21 can't even remember the character. I think it  
22 was Hotspur was bragging that "I could call

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1 the spirits from the vasty deep." And his  
2 friend said, "Yes, but when you do call upon  
3 them, will they come?"

4 (Laughter.)

5 I think we're a little bit in that  
6 mode at this point.

7 So, if there are no further  
8 comments from the group, I think it would be  
9 appropriate to turn to public comments at this  
10 point in time.

11 And I have just been given a note  
12 that says no members of the public have signed  
13 up for comment.

14 So, is there anyone in the room  
15 who does want to say anything?

16 (No response.)

17 If not, let me just note for the  
18 record that the legislation that created this  
19 group asks that we seek comments from all  
20 constituencies, and certainly including the  
21 broad public. We have had many comments  
22 previously, and I guess everyone has said what

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1           they have to say.

2                       So, we will proceed.

3                       Harold?

4                       MEMBER VARMUS: Can I just ask --  
5           we have had a lot of discussion about  
6           Recommendation 1, but to my amazement, there's  
7           been no comment on Recommendation 3, which has  
8           always been a major sticking point around the  
9           IC Directors' table.

10                      MEMBER           RUBENSTEIN:           That's  
11           certainly true.

12                      MEMBER VARMUS: Maybe we should  
13           focus for a moment on how we would pay for the  
14           Clinical Center and see. I, myself, am happy  
15           to sign up for that. I think it's a pretty  
16           good solution. But does anyone else think  
17           that?

18                      MEMBER RUBENSTEIN: I would say,  
19           before you came, we had innumerable  
20           discussions and a lot of debate about the pros  
21           and cons of it. So, it's just you weren't here  
22           to hear about, but as you would have

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1 predicted, it was a very, very big issue.

2 (Laughter.)

3 And I think the compromise, which  
4 we should hear people's opinion about, wasn't  
5 the only possibility or necessarily one that  
6 everyone thought was the best at the  
7 beginning.

8 I think in terms of what we  
9 thought we could get done and the most  
10 practical thing at this time without enormous  
11 political and other issues -- I think we all  
12 coalesced around it. But, there are opinions,  
13 both in the full SMRB and our Work Group, and  
14 I think I would advise people to respond to  
15 Harold. It was a good discussion that we have  
16 had for many, many weeks.

17 MEMBER FAUCI: Yes, Harold, there  
18 were five issues. The first two were either  
19 as-is or a modified version of as-is. We all  
20 agreed that was out; that didn't work.

21 The other three: individual  
22 institutes, in the OD, separate line item.

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1 Individual institutes would only have a  
2 problem with pitting one against the other.

3 MEMBER VARMUS: And we don't want  
4 that.

5 MEMBER FAUCI: We don't want that.  
6 Okay.

7 (Laughter.)

8 The other one, a line item, too  
9 much at the control and manipulation of  
10 congressional issues.

11 The other one was OD. That's how  
12 we -- I mean it took us about five months.

13 (Laughter.)

14 MEMBER VARMUS: Thank you for the  
15 summary.

16 MEMBER KATZ: So, in fairness to  
17 Tom Kelly, who's not here, I think Tom  
18 repeatedly brought up the concern about this  
19 increment that came from the extramural funds.  
20 That is why we put together this table,  
21 actually, because he was very concerned, as he  
22 was concerned with the original Roadmap funds

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1 or Common Fund, that it was going to take a  
2 lot of money from the Extramural Program, yes.

3 MEMBER VARMUS: Well, (a) it's not,  
4 but (b) the fact that there's some does send  
5 the signal that the extramural community is  
6 involved, and should be involved.

7 MEMBER KATZ: Absolutely. But I  
8 bring it up because Tom isn't here and he  
9 brought it up every single time.

10 (Laughter.)

11 And I just wanted to make sure  
12 that his view was seen at the table.

13 MEMBER RUBENSTEIN: I think it was  
14 always clear, as Tony very specifically said,  
15 there was confusion at the beginning when we  
16 talked about what kind of amount of money  
17 would be necessary to be added from outside  
18 the Intramural Program.

19 When we tried to make it exactly  
20 clear by that table and the very capable  
21 analysis, it was not a lot of money from the  
22 total NIH budget. In fact, as Tony said, it

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1           may be a minuscule amount of money.

2                       But, in principle, it was an  
3           important change. Of course, if the  
4           opportunity over years comes that we have to  
5           put in some more money, there was a  
6           straightforward mechanism that in the overall  
7           NIH budget was still pretty tiny. It seemed  
8           like a reasonable solution.

9                       Gail may want to talk about her  
10          view, because we debated that a lot as well.

11                      MEMBER CASSELL: Well, thank you,  
12          Arthur.

13                      I guess I was the lone voice that  
14          suggested that the direct line appropriations  
15          from Congress would be a good way to go. But  
16          Tony, my friend, convinced me otherwise. It  
17          took a few meetings, but I'm in agreement with  
18          the recommendation here.

19                      I think that we did spend an awful  
20          lot of time on the budget issue, and this is  
21          what we came up with. I really like the  
22          graphic showing the spectrum of options. I

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1 think it is very clear now, and also the  
2 table.

3 And with that, I would hope that  
4 people think that this was the best decision  
5 of all the potential options.

6 CHAIR AUGUSTINE: Excuse me. I saw  
7 Francis and then Bill.

8 DIRECTOR COLLINS: So, I just  
9 wanted to ask for any more information you  
10 might be able to offer about the governance  
11 model, because we haven't talked about that.

12 I certainly agree that the way in  
13 which things have been overseen is complex,  
14 unnecessarily so, and potentially duplicative.  
15 And the model you put forward streamlines a  
16 lot of that effort.

17 I am just wondering if you have in  
18 your deliberations made any kind of inroads  
19 into what is the charge to the proposed  
20 Clinical Center Governing Board of IC  
21 Directors, since that's sort of a new entity  
22 here. I'm not asking you to get into the weeds

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1           here, but if you have sort of a general  
2           concept of that group's role versus the ABCR?

3                   MEMBER RUBENSTEIN: Tony, did you  
4           want to comment on that? Steve?

5                   MEMBER KATZ: Why don't I comment  
6           on that?

7                   MEMBER RUBENSTEIN: Yes.

8                   MEMBER KATZ: The thought is that  
9           that group is going to serve as advisory to  
10          you. That group will serve to provide a  
11          context for what the other demands are on the  
12          NIH budget. So that, as the current Management  
13          Budget Work Group works to advise you, it's  
14          going to advise you, and in the context of  
15          what the budget allocation is anticipated from  
16          the Congress.

17                   So, for example, the ABCR; we've  
18          actually tried to get specifically how much  
19          the ABCR has advised in the past. They have  
20          had the constraints of being told they can  
21          only advise a certain amount, because that's  
22          what the budget is going to be. But if they

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1           advise a 15 percent increase to keep up with  
2           inflation for clinical research, and the NIH  
3           is getting a 1 percent budget increase, we  
4           felt that it would be important for you to  
5           have a group of IC directors who could put it  
6           in some context, but it will ultimately be  
7           your decision.

8                       But, basically, what this does is  
9           it removes this financial -- this budget item  
10          from the other competing priorities of the ORS  
11          and the other central services. Basically, it  
12          sets it apart.

13                      But the group that's advising you,  
14          the IC Directors, are advising you in the  
15          context of the total budget.

16                      CHAIR AUGUSTINE: Bill or Tony, do  
17          you want to add anything?

18                      MEMBER FAUCI: No. Steve said it  
19          quite well right now.

20                      CHAIR AUGUSTINE: Bill?

21                      MEMBER ROPER: I'm not sure this is  
22          a useful comment, but I'll make it anyway.

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1 Harold is right to say that we shouldn't focus  
2 only on the finances; there are many other  
3 even more important issues.

4 But as we have been talking about  
5 the finances, I'm struck with the parallels  
6 between this and the debate that's gone on for  
7 decades around the country in various  
8 metropolitan areas about how to pay for  
9 municipal transit systems and the right  
10 balance between riders of those systems  
11 bearing the costs and whether there would be a  
12 general tax on the populace to fund the  
13 system.

14 The Metro system that I rode  
15 yesterday wouldn't exist if there weren't a  
16 general tax on the people of this metropolitan  
17 area, but there's always the debate.

18 If that's too much, then it will  
19 be bloated, and the Tea Party movement -- you  
20 don't need me to tell you what they would have  
21 us do with these kinds of things.

22 On the other hand, if the cost on

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1 individual riders is too high, they will find  
2 other ways to get to work, and they will not  
3 ride Metro. So, there are a lot of parallels,  
4 it seems.

5 MEMBER RUBENSTEIN: Just one  
6 comment. It was also clear -- and I think,  
7 again, it is a response to a legitimate  
8 question from Harold -- that these advisory  
9 committees would be able to prioritize  
10 clinical research, because not everything can  
11 be done by everyone. That is obvious. There's  
12 just not enough money, and maybe some of it  
13 isn't worthwhile doing in terms of quality.

14 So, part of the input here is our  
15 oversight of the programs in the Clinical  
16 Research Center and how they would be  
17 prioritized and adjudicated in terms of  
18 investigator requests, and so on.

19 So, there was a really important  
20 role, and these two bodies, the ABCR, if I've  
21 got that right, and the Intramural Research  
22 Program Directors, would have significant

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1 input in terms of advisory to you in terms of  
2 that regard, too, as well as the budget  
3 issues.

4 CHAIR AUGUSTINE: Any other  
5 comments?

6 (No response.)

7 Hearing none, I mentioned before  
8 we got into the topic that there are a couple  
9 of complicating factors that are probably  
10 apparent to most everyone at the table.

11 One of the complicating factors is  
12 the work of the TMAP group that's now  
13 underway, the Translational Medicine Group,  
14 clearly could have an impact on how you handle  
15 the Clinical Center, and particularly its  
16 budgeting.

17 If we take some decisive action on  
18 the recommendations we have just heard, we may  
19 in December of this year, when the TMAP group  
20 completes its work, discover that we put  
21 ourselves in a box of some type.

22 And in terms of the rigidity of

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1           that box in which we could place ourselves, or  
2           more specifically place Francis and his  
3           colleagues, it is that under the law that  
4           creates the SMRB, if we make a recommendation,  
5           it triggers a number of events with specific  
6           time scales specified in the law.

7                       For example, if Francis accepts  
8           our recommendations, he has to begin  
9           implementing them within a certain number of  
10          days and begin submitting reports as to the  
11          status of the implementation, which I know he  
12          looks forward to, but --

13                       (Laughter.)

14                       DIRECTOR COLLINS: That's what gets  
15          me up in the morning.

16                       CHAIR     AUGUSTINE:     Yes,     that's  
17          right.

18                       But, anyway, it triggers events  
19          that we, all of us, have no control over.

20                       Secondly, if Francis decides not  
21          to proceed with our recommendations, he then  
22          is obliged within a certain number of days to

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1 submit an even longer report, probably  
2 -- (laughter) -- to the public and the world  
3 saying why he thinks we're off-base.

4 And so we kind of are in this trap  
5 where, until December, we're not really  
6 prepared, my personal view, I don't believe  
7 we're in a position to take a decisive action  
8 here. And if we attempted to do so, we would  
9 trigger a no-win circumstance, I think, in  
10 either direction. Again, that is a personal  
11 opinion, but I think it is shared by others  
12 I've talked with.

13 Fortunately, the way that Arthur's  
14 group has made their recommendations lends  
15 itself to a way out of this box. For example,  
16 Recommendation 2, that the current  
17 organizational structure is not adequate, that  
18 we need a new, more streamlined structure,  
19 that is not a specific enough recommendation,  
20 I'm advised by our counsel, to trigger all  
21 these events.

22 But the group also went to the

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1 next step and said how you should organize, in  
2 our view, to deal with this issue. That does  
3 trigger it.

4 The third recommendation, where we  
5 say that the current funding approach is not  
6 viable, no problem. We say what you want is a  
7 line-item approach in the OD budget. That does  
8 trigger it.

9 So, one way we could handle this,  
10 if the committee chose to, would be today to  
11 vote on the report of the committee in terms  
12 of the overarching principles that it has  
13 proposed, such things as greater external use,  
14 more streamlined organization, a more viable  
15 or a viable funding approach for this new  
16 usage, and leave the specific details to be  
17 addressed in December, at the same time as we  
18 address the TMA report, and then submit the  
19 TMA report and this report at the same time.  
20 Fortunately, December is not that far away,  
21 and we have a meeting scheduled then.

22 That's one way to deal with this.

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1           There may be other ways that are better.

2                       So, let me just open the floor to  
3 anybody who wants to comment on that.

4                       Steve?

5                       MEMBER KATZ: Norm, I think your  
6 recommendation is fine, because Francis can  
7 actually implement a change in governance  
8 without actually hearing from this group at  
9 all. So, I think part of this could be  
10 implemented, if you like it, and it would not  
11 preclude what the future recommendations will  
12 be.

13                      CHAIR AUGUSTINE: Other comments?

14                      MEMBER VARMUS: I don't hear any  
15 disagreement with the specific recommendations  
16 that have been made. So why not endorse the  
17 report?

18                      CHAIR AUGUSTINE: I take that as a  
19 motion?

20                      MEMBER VARMUS: Yes.

21                      CHAIR AUGUSTINE: Is there a  
22 second?

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1                   MEMBER FAUCI: Would it be out of  
2 form to ask, Francis, what do you think would  
3 work best for you?

4                   DIRECTOR COLLINS: Well, I  
5 appreciated Norm's articulation of the issue.  
6 We do have this TMAP process which we're going  
7 to be talking about today and tomorrow, and  
8 which is on a short timeline, by December, to  
9 try to look more broadly at our efforts in  
10 translational medicine and therapeutics.

11                   One possible consequence of that  
12 might be some organizational recommendations  
13 that would involve the Clinical Center, the  
14 CTSAs, perhaps what is going on with the Cures  
15 Acceleration Network, with TRND, with RAID,  
16 with our Molecular Libraries Program, and this  
17 whole pipeline for therapeutic development.

18                   And I would think, therefore, that  
19 to make a very specific recommendation about  
20 precisely where you want the Clinical Center  
21 budget line, for instance, to land -- while it  
22 seems very thoughtful, what you have come up

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1 with at this point, I'm not sure that without  
2 going through that process over the next three  
3 months that you would be absolutely confident  
4 that the answer is going to be the same.

5 So, I like the recommendations the  
6 way they are phrased because, as Norm has  
7 said, they are rather general, and they do  
8 capture the sense of the major changes that  
9 need to be made.

10 But I think, as Norm has also  
11 pointed out, it might present some awkwardness  
12 by triggering timelines to get down into the  
13 specifics of that in terms of exactly how the  
14 governance would be set up or exactly where  
15 the budget line for the Clinical Center would  
16 be.

17 I would find it easier to have  
18 those recommendations of the more specific  
19 sort delayed until December.

20 CHAIR AUGUSTINE: Steve, were you  
21 going to say something?

22 MEMBER KATZ: No, I was just going

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1 to reiterate, if we do approve the report,  
2 then you can implement whatever part of the  
3 report you want.

4 CHAIR AUGUSTINE: We would approve  
5 the report in principle. We would not be  
6 saying at this point go ahead with the line-  
7 item funding, and so on.

8 Harold, you've got your light on  
9 there.

10 MEMBER VARMUS: Well, Tony was  
11 about to make a comment.

12 MEMBER FAUCI: I am a little bit  
13 slightly confused. And that is that we are  
14 going to approve the report but not make  
15 formal recommendations? Is that what you're  
16 saying?

17 CHAIR AUGUSTINE: No, I think I  
18 would word it a little differently, Tony.

19 MEMBER FAUCI: Okay.

20 CHAIR AUGUSTINE: I think I would  
21 say that we are going to approve the  
22 overarching principles cited in the report,

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1 but we will not approve the report until  
2 December.

3 MEMBER FAUCI: I got it. Okay.

4 MEMBER VARMUS: Well, I'm still a  
5 little -- I'm not actually clear about how you  
6 imagine, Francis, that these recommendations  
7 would be changed by any of the TMAP  
8 discussion. I suppose it is conceivable, but I  
9 think the committee has done its work. There  
10 is consensus; there are some very useful  
11 recommendations. The Director does have the  
12 opportunity to disagree with them and even  
13 represent a case for not implementing them.

14 But it seems to me we sort of  
15 weaken our position as a group by saying,  
16 well, you know, in general, we are endorsing  
17 the report that we've done so much work on,  
18 but we don't actually endorse all the  
19 specifics.

20 CHAIR AUGUSTINE: Harold, so what  
21 you are arguing is your own motion here.

22 (Laughter.)

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1                   MEMBER VARMUS: No, I'm arguing for  
2 approving it. Yes.

3                   MEMBER FAUCI: But, Norm, if we  
4 make the recommendation -- and again, to me,  
5 it's just what works best for Francis -- but  
6 it seems to me that, given all of our  
7 deliberations, if we make the recommendations,  
8 and what happens in December with the other  
9 group is a reason to modify them some, then  
10 since they're only recommendations to Francis,  
11 Francis can say, "I understand your  
12 recommendations, but I want to change them a  
13 little, in light of what we're talking about  
14 with the translational medicine."

15                   Is that what you mean, Harold?

16                   CHAIR AUGUSTINE: I think the  
17 concern is that, if we just approve the  
18 report, we trigger all these legal events that  
19 you've got to deal with that we would rather  
20 avoid until December.

21                   DIRECTOR COLLINS: That is the  
22 concern. Let me be a little more specific.

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1                   So, for instance, suppose the TMAP  
2                   recommendation is to come up with a new  
3                   organizational structure that would capture  
4                   what we're doing in translation. Then that  
5                   would lead to the conclusion that having the  
6                   Clinical Center budget line in OD is maybe not  
7                   the optimum solution, once you come up with a  
8                   more integrated pathway for therapeutics. I  
9                   don't know if that's where TMAP may go, but  
10                  it's one of the possibilities on the table, as  
11                  we have talked about.

12                 If you approve this report  
13                 including the details right now, then we may  
14                 have ourselves in a little bit of a pickle, or  
15                 I may be in a pickle, because then I'm  
16                 required, as you have heard, to go through  
17                 this legal process of either agreeing or  
18                 disagreeing with reports and paperwork and so  
19                 on.

20                 It would be, I think, more facile  
21                 in terms of getting all of these deliberations  
22                 to a good endpoint to have this group approve

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1 the principles of your report, which I agree  
2 are superb, and that includes the  
3 recommendations themselves. Because if you  
4 look at them carefully, they're written in a  
5 general sense. But to delay approving the  
6 entire report in terms of the details until  
7 December, at which point we may have some more  
8 information that might cast some light on this  
9 -- that is the subtlety I'm trying to capture,  
10 and it doesn't look like it's been captured.

11 CHAIR AUGUSTINE: Excuse me. I saw  
12 Arthur, and then Harold.

13 MEMBER RUBENSTEIN: You know, I  
14 don't know the exact regulations, but one  
15 possibility would be just, seeing there seems  
16 to be a consensus, to delay the vote on the  
17 report until December. Then we don't have to  
18 have all this Mickey Mouse about what we are  
19 approving and what we're not.

20 That just seems to me -- we don't  
21 need to go back and revisit the report,  
22 because everyone seems to at least be

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1           supportive, and just let's say in three months  
2           it will come up for a vote.

3                   MEMBER VARMUS: Right. That's the  
4           point I was going to make. I don't know how we  
5           separate the principles from the details,  
6           because the principles are in the details.

7                   CHAIR AUGUSTINE: I think that  
8           works fine. Okay.

9                   Are there any further comments?

10                   (No response.)

11                   I assume that was your motion.

12                   (Laughter.)

13                   Gene, I assume that was your  
14           second.

15                   Okay, all those in favor of  
16           tabling the motion until December, please say  
17           aye.

18                   (Chorus of ayes.)

19                   Those opposed?

20                   (No response.)

21                   That was overwhelming. Okay.

22                   We're a little bit ahead of

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1 schedule, and we have some people who are  
2 going to participate in the next session who  
3 won't be here for about 10 more minutes.

4 So, why don't we take our break at  
5 this point? We're scheduled for a 15-minute  
6 break, if everybody could be back promptly.  
7 Thank you.

8 (Whereupon, the foregoing matter  
9 went off the record at 9:22 a.m. and went back  
10 on the record at 9:41 a.m.)

11 CHAIR AUGUSTINE: If everyone would  
12 take your seats, we can begin again.

13 Okay. During the break, I was  
14 thinking that a week ago today I was tracking  
15 gorillas in Rwanda. The more I think about it,  
16 the better preparation for this meeting it  
17 was.

18 (Laughter.)

19 Now we'll turn to the subject for  
20 the rest of today, which is the work of the  
21 new group on translational medicine and  
22 therapeutic discovery. That group, as we have

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1 mentioned, will be chaired by Arthur because  
2 of the close tie we have already discussed to  
3 the work he has just shared on the Clinical  
4 Center.

5 So, Arthur, we'll kind of turn to  
6 you to carry on here. We will have a couple of  
7 speakers just sort of introduce the topic, and  
8 then we have a terrific panel for a panel  
9 discussion. The rest of the day will be  
10 devoted to this topic.

11 Arthur?

12 MEMBER RUBENSTEIN: Thanks, Norm.

13 My colleagues at Penn want to know  
14 why I'm doing all this work for the NIH, and  
15 when I couldn't give them the explanation,  
16 they got rid of me.

17 (Laughter.)

18 So, I do want to say it is a labor  
19 of love, but it has consequences. So, there we  
20 are.

21 Anyway, it is a subject I believe  
22 in strongly, so I'm happy to do it.

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1                   We also have some colleagues from  
2 Penn here, particularly Garret FitzGerald and  
3 others.

4                   We have thought about this subject  
5 for a very long time. Of course, with Francis'  
6 leadership and involvement in it, it does seem  
7 a very, very worthwhile issue to evaluate  
8 carefully at this time.

9                   So, on your behalf, and  
10 particularly all the excellent invitees that  
11 we have who, I think, will be the key people  
12 to listen to, we should, I think, learn about  
13 and think about how to move this important  
14 subject forward.

15                  So, today I would like to frame  
16 the discussion by providing you with a brief  
17 overview of the charge to the group. This  
18 charge has two principal components, and these  
19 are listed on the slides for you, and they're  
20 in your book as well.

21                  I would ask you to look at them  
22 carefully, because it will consume our

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1 attention for the next three or four months,  
2 because there is a short timetable, and the  
3 issues are very important.

4 So, we wish to identify the  
5 attributes, activities, and capabilities of a  
6 translational medicine program, particularly  
7 to advance therapeutics, which I think there  
8 is general agreement around the world that  
9 there is some lack of movement in terms of the  
10 opportunity for developing new therapeutic  
11 agents, and so on.

12 And broadly assessed from a high-  
13 level view, the NIH landscape for these  
14 programs, networks, incentives for inclusion  
15 in this network, and think about the optimal  
16 organization.

17 And of course, it is in that  
18 regard that the Clinical Center, which is or  
19 could be a key part of this, we delayed the  
20 final recommendations in that regard.

21 Here is the group. It involves the  
22 original group, but it expanded appropriately

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1 to involve people with a variety of knowledge  
2 and expertise. I won't read through all their  
3 names, but, again, it is also in your book.  
4 And there will be a lot of input from outside  
5 as well as the committee group themselves.

6 So, the considerations that  
7 Francis has asked us to think about carefully  
8 on behalf of the SMRB is to consider how the  
9 agency could leverage and organize a wide  
10 range of resources to implement the Cures  
11 Acceleration Network, which is part of the new  
12 healthcare bill.

13 In addressing this change, our  
14 responsibilities are to look at the current  
15 NIH infrastructure and initiatives which may  
16 have relevance to the therapeutic development  
17 pipeline and to synergize and avoid  
18 competition with resources in the private  
19 sector.

20 A key part of this was to  
21 coordinate and synergize with the private  
22 sector rather than compete with them. And I

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1 think that was made very clear in Congress in  
2 the bill and, of course, there's a mandate  
3 that we are very sensitive to.

4 Our Work Group in the next three  
5 or four months will consider recommendations  
6 for strengthening the Clinical Center -- we  
7 have discussed that in detail -- as well as  
8 other recommendations by a variety of informed  
9 bodies, particularly the Institute of Medicine  
10 report.

11 But there have been numerous  
12 reports that we actually looked at carefully  
13 as we looked at the program for the Clinical  
14 Center, and we have as well evaluated and will  
15 look at them again, so that we don't just try  
16 to reinvent the wheel.

17 And we would also like to have  
18 some methodology and metrics that can be used,  
19 so that we just don't come up with things that  
20 have little impact, but that we can evaluate  
21 and measure what we recommend if this group  
22 implements it and the NIH puts them into

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1 practice.

2 So, this TMAT group will recommend  
3 to the full Board in their report issues  
4 related to the following big areas: The  
5 attributes, activities, and the functional  
6 capabilities of a translational medicine  
7 program.

8 So, are there any changes,  
9 organizational structures, or budget issues  
10 that could be modified that would make this  
11 program more streamlined, advantageous, and  
12 successful?

13 We would hope to come up with some  
14 recommendations to organize the existing  
15 components, to optimize their relation to each  
16 other and the organization, and then methods  
17 for evaluating successful or untoward  
18 consequences, as I have described to you  
19 before.

20 So, that's just a framework. The  
21 big issue is really, is there a more  
22 effective, advantageous way of organizing

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1 translational medicine and therapeutics,  
2 starting within the NIH but involving the  
3 agencies around the country and the private  
4 sector as well, that could move this subject  
5 forward in a way that would create successes  
6 for all of us in a way that we would be  
7 pleased about?

8 So, we have a variety of sessions  
9 outlined here where there will be some  
10 presentations and a group of distinguished  
11 visitors. I do want to just say, on behalf of  
12 everyone -- and I know others will comment --  
13 how pleased and delighted we are that people  
14 have made time in their busy schedules to  
15 come. And many people have given up other  
16 opportunities for the need to come here today  
17 and tomorrow, and we just want to thank you  
18 and say how pleased we are about that.

19 So, there will be, overall, four  
20 sessions today and tomorrow -- thinking about  
21 advice and ideas and creative thinking about  
22 this opportunity. Then, after that, the Work

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1 Group will deliberate and think about how to  
2 proceed and advise Francis about possibilities  
3 in this area.

4 I think I'll stop there and answer  
5 any questions. Norm?

6 (No response.)

7 I think that's how I'll end, and  
8 if there are no questions, we could just get  
9 on with the presentations.

10 So, the way the program is  
11 organized, we have two talks -- the first by  
12 Charles Baum and then by Jesse Goodman. Then,  
13 after that, we have a panel discussion, and  
14 that will take the morning session. And I  
15 think there will be time for a significant  
16 input both from the SMRB and the public.

17 So, the first -- we have asked  
18 Charles Baum, who is the Senior Vice President  
19 for Clinical Programs at Pfizer, to talk on  
20 the current landscape of drug discovery and  
21 opportunities for new paradigms.

22 And we are grateful for your

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1 coming and appreciate your comments.

2 DR. BAUM: Well, thank you for the  
3 invitation.

4 And it's a very important topic to  
5 us; the role of translational medicine and the  
6 key part that that is going to play going  
7 forward for all of us in the development of  
8 new therapeutics.

9 Obviously, this is a broad topic  
10 that covers a lot of ground, and we could  
11 probably spend days talking over this topic.  
12 But I'm going to focus the discussion around  
13 some of the things that we have done at our  
14 institution, at Pfizer, to try to address some  
15 of the challenges of drug discovery and  
16 development as a paradigm that we could talk  
17 about, and I welcome questions along the way  
18 on how we've done it. Certainly, we don't have  
19 all the answers, but we're looking for  
20 additional collaborations.

21 Someone is in my pocket.

22 (Laughter.)

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1 I'm not used to that happening.

2 So, let's get started.

3 I think everyone is well aware of  
4 this topic, and there has been a tremendous  
5 amount of discussion about research and  
6 development productivity in all aspects of  
7 development, but especially in the  
8 pharmaceutical industry and how we are doing  
9 over time. Certainly, there's a number of  
10 great therapeutic advances that have occurred,  
11 but there's also, obviously, tremendous room  
12 for improvement.

13 And one of the indications of that  
14 room for doing better is shown here. And it  
15 indicates that, despite a huge increase in  
16 spending on our part to find new useful  
17 therapeutics, that we have ended up with  
18 roughly the same number of approvals of new  
19 molecular entities over this 20-year period,  
20 with probably a tenfold or so increase in  
21 money being expended. So, something in the  
22 model wasn't working, and we needed to change

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1           it.

2                       I can show you now some of the  
3 things we have done to change this, both in an  
4 organizational sense, but also in the research  
5 -- how we conduct research and the culture of  
6 how we do that work.

7                       So, this is an obvious slide that  
8 many of you have probably seen before. The  
9 cost of bringing a program from early stages  
10 of discovery through to patients is probably  
11 on the order of \$100 million. It varies  
12 somewhat, but that's probably an average for a  
13 successful program.

14                      The problem is really on the right  
15 side, where you see that a huge amount of our  
16 expenditures are in projects that fail. So,  
17 what we need to do is really get a better  
18 sense of why those projects are failing and do  
19 a much better job of making them fail sooner  
20 rather than later.

21                      So, we need to identify in  
22 research in Phase I and Phase II which

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1 projects are those that are most likely to  
2 succeed and those which aren't and to kill  
3 those that aren't as early as possible. And  
4 there's a key role for translational medicine  
5 and translational research in that area.

6 So, just in terms of our evolution  
7 over this time period -- over the last decade,  
8 roughly, in the years up to about 2008 --  
9 there was a great expansion in our research  
10 and development organization. We had many  
11 sites spread across a number of countries.  
12 There was a fair amount of autonomy at these  
13 sites. There were a lot of overlapping efforts  
14 and efforts that weren't coordinated together  
15 and a very bureaucratic organization that had  
16 many levels between the CEO and the bench  
17 scientists. So, a lot of the messages weren't  
18 getting through.

19 Obviously, there were a lot of  
20 measurements and metrics, but those were  
21 mostly metrics of activity. So that we had a  
22 large number of candidates coming through the

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1 pipeline and a large number of Phase III  
2 programs, but that was the goal -- the  
3 numbers, to maximum the numbers -- rather than  
4 focus on the human biology, the human  
5 genetics, and really what were the most  
6 impactful projects and focus our efforts  
7 there.

8 The organization was made up of  
9 large groups of scientists of up to 1,000  
10 people in some cases. Working on some of these  
11 projects are very large and bureaucratic  
12 groups. It took them a while to make  
13 decisions. They tended to be slow and  
14 bureaucratic, and that is something that  
15 slowed down progress but also slowed down  
16 decision-making.

17 We also had no formal scientific  
18 advisory board on the outside. That is  
19 something that was definitely a change from  
20 current expectations.

21 And 90 percent of our work was  
22 conducted in-house. So, Pfizer was a very

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1 internally-focused company. We looked to the  
2 inside for all of the answers. I think that's  
3 a dramatic change there that we'll talk about  
4 in a few slides.

5 And probably one of the biggest  
6 changes, from all of our activity being  
7 internal to about a third of the activity is  
8 now being conducted in collaboration with  
9 external institutions, academic institutions,  
10 biotech companies, and other pharma companies.  
11 And this issue that was discussed earlier  
12 around intellectual property, how do we work  
13 with that? How do we make a more open and  
14 collaborative environment as we go forward?

15 So, basically, the organizational  
16 changes we made were to simplify the  
17 organization, to make decision-making easier,  
18 quicker, and make it based on the science and  
19 about validity to the patient. That could be  
20 in huge areas of unmet need, but also in rare  
21 diseases.

22 And there's been a new focus --

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1 we'll mention briefly -- but ongoing, in rare  
2 diseases, and focusing not just on the overall  
3 population, but on subsets of patients that  
4 will be identified through our efforts in  
5 human genetics and translational medicine.

6 So, in breaking down the  
7 organization into much smaller research units,  
8 those research units are led by a Chief  
9 Scientific Officer who's local and can make  
10 decisions with a group of researchers of 100  
11 to 200, roughly. And that group is focused  
12 entirely on a particular area of focus - a  
13 therapeutic area for the most part. They share  
14 that vision; they share ownership of the  
15 project. So, you have a much different kind of  
16 culture and a much different kind of feel --  
17 much more like a small group, a small company,  
18 a biotech company in some cases -- that  
19 provides not just greater motivation and a  
20 different culture, but also the ability to  
21 move quicker, make decisions quicker.

22 And those decisions could be to go

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1 forward, but also to cut projects. And the  
2 rewards should be there for cutting projects  
3 that are not productive, again, so that we  
4 improve our chances of success and decrease  
5 attrition in late-phase, which is where all of  
6 our expenditures of resources occur. So, the  
7 key part of this is not just structure, but  
8 how we conduct ourselves.

9 This is just an example of the  
10 organization. And it shows that these groups,  
11 led by CSOs in each of these areas, are  
12 focused on particular therapeutic areas and  
13 that those areas are supported by a large  
14 infrastructure that provides all of the  
15 necessary parts for drug development -- so,  
16 medicinal chemistry, a variety of approaches  
17 to biotherapeutics, and all of the parts of  
18 the organization you need to support the CSOs  
19 and these groups to be able to maximize the  
20 benefit of their science and to bring these  
21 new therapeutics forward as quickly as  
22 possible.

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1                   And I won't talk much about this,  
2                   but the other part of the organization that is  
3                   also changed is on the commercial side, where  
4                   we have separated the business into business  
5                   units, and those units are, again, specific to  
6                   particular areas -- the most relevant ones,  
7                   for research and development, where we feed  
8                   most of our projects into primary care,  
9                   specialty care, and oncology.

10                  So, there's very close bonds  
11                  between those groups. And these groups and the  
12                  business units take the projects from proof-  
13                  of-concept stage through Phase III and through  
14                  post-marketing development.

15                  So, in terms of how we have  
16                  conducted a traditional discovery paradigm,  
17                  the focus was on picking a target, picking a  
18                  molecule, and optimizing the chemistry, and we  
19                  became very good at that and then do the  
20                  clinical testing.

21                  But it was a linear process. So,  
22                  you would go forward, generally throwing it

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1 over the fence at each stage, and not enough  
2 interaction forward as well as backwards. So,  
3 with the interactions of research with  
4 clinical and the interactions of clinical back  
5 with research, based on the clinical outcomes,  
6 it was not what it should be.

7 We think that's one of the key  
8 areas that needs to occur, so that there's  
9 more interaction, more learning coming from  
10 our clinical expertise and clinical experience  
11 and the huge amount of data in those clinical  
12 trials -- even if those trials are negative --  
13 that we can learn from in deciding the next  
14 studies and learn from in terms of patient  
15 segmentation and identifying the appropriate  
16 patient population for the next programs or  
17 modifying the population for the existing  
18 program to make it more likely to succeed.

19 So, the way we want to think about  
20 that process now is more of an iterative  
21 process and focusing on the best target, as  
22 defined by the best biology. So, focusing on

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1 human biology and human genetics to help us  
2 define what the best targets are early on in  
3 the process from the very beginning, and also  
4 to focus on the human condition. What is the  
5 disease, the patient population that we're  
6 looking to study, and getting that into the  
7 lab as early as possible, so that we're  
8 addressing the right question from as early as  
9 possible.

10 Then we have the opportunity to  
11 design the best small or large molecule. We  
12 have a lot of expertise in chemistry and  
13 designing the small molecules, but also a  
14 large expertise not only in biotherapeutics  
15 and the ability to bring all of those  
16 different techniques to bear on a particular  
17 clinical problem, so that we find the best  
18 solution, not just the solution that's most  
19 convenient.

20 Another part of this is that this  
21 requires, this whole process requires  
22 extensive collaboration, and I'll mention that

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1 as well, with both internal and external  
2 experts.

3 So, really, the take-home lesson  
4 here on our side of what needs to be different  
5 going forward is a focus on human biology and  
6 on human genetics to define the best patient  
7 populations and the appropriate way to treat  
8 those diseases.

9 So, as I mentioned, obviously,  
10 stem cell biology, cell biology in general, as  
11 well as human genetics are key components of  
12 what we believe to be a foundation for  
13 translational medicine, personalized medicine,  
14 along with all of the other attributes,  
15 molecular profiling, systems biology, and  
16 bioimaging, which all together create the  
17 right profile for the patient, selecting the  
18 right target and the right patient to increase  
19 our opportunities for success with these  
20 programs.

21 So, these are the areas, the key  
22 areas, of focus for us and for many other

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1 groups. But it illustrates the need in many of  
2 these cases to focus on the right patients.

3 For example, we have extensive  
4 effort in immunology and inflammation. But in  
5 the past, that was focused almost entirely on  
6 rheumatoid arthritis and treating the whole  
7 population of patients. We are making  
8 significant efforts now to look at subsets of  
9 patients with rheumatoid arthritis, but also  
10 patients with lupus and with other autoimmune  
11 diseases to see if those patients will give us  
12 insight into treating subsets of patients more  
13 effectively, but also treating the larger  
14 patient population with inflammatory diseases  
15 more effectively.

16 So, patient segmentation, as I've  
17 already mentioned a number of times, is key to  
18 our programs going forward. So, this is an  
19 opportune time, actually, with a big emphasis  
20 in our institution, but I think across the  
21 board, in how do we better select the  
22 patients. How do we better understand the

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1 targets, based on human genetics as well as  
2 the biology and human systems, so that we can  
3 select the best targets better sooner?

4 And the disease understanding is  
5 the key point to making the overall process  
6 more effective, resulting in higher  
7 probability of success, but also in  
8 terminating projects earlier. So, the better  
9 we can make decisions in Phase I and Phase II  
10 to stop programs that are not showing the  
11 kinds of effects we want to see -- because we  
12 can focus on the right patients, and if in  
13 those patients we don't see an effect, then we  
14 should move on to a different focus for that  
15 program or just stop the program. That allows  
16 us to move much more quickly, we feel, towards  
17 the real solution a more effective  
18 therapeutic.

19 Ultimately, it results in a better  
20 therapeutic index, a better benefit-to-risk  
21 ratio for the patients, for the payers, and  
22 for the system in general.

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1                   So, I thought I would show a  
2                   couple of examples of patient selection that  
3                   have been relevant to recent years here. One  
4                   is in lung cancer patients, which tended to be  
5                   treated as a group without looking at patient  
6                   subsets very effectively.

7                   We started a program quite a few  
8                   years ago called crizotinib. It's an oral  
9                   selective inhibitor of MET and ALK. And  
10                  actually, our focus for the program was MET in  
11                  addition, because it seemed to play a role in  
12                  a number of different solid tumors.

13                 So, we took that program forward  
14                 into Phase I. During the Phase I program, we  
15                 discovered, with the help of academic  
16                 collaborators, that 10 percent or so of non-  
17                 small cell lung cancer patients had a  
18                 translocation of the ELM4 ALK, which  
19                 upregulated expression. And those tumors were  
20                 dependent on that mechanism.

21                 So, we modified the clinical  
22                 program. I think it's important to show that

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1           you can do that in an iterative way, if you're  
2           keeping your eye on the literature, adding  
3           patients to that initial first Phase I, but,  
4           then, re-engineering that Phase I to focus on  
5           those patients.

6                       And through doing that, we found a  
7           very high response rate that you could see  
8           very quickly in that small patient population,  
9           because the overall response rate was in the  
10          order of 65 percent. So, it was pretty easy to  
11          identify that quickly, see it, and act  
12          appropriately to start planning for a future,  
13          to expand the program and to move it along,  
14          but, also, to start discussions with  
15          regulators around the world to see how that  
16          could be developed collaboratively.

17                      And in many of these cases, we  
18          found that the agency and other health  
19          authorities have been very helpful, actually,  
20          in working with us to bring these projects  
21          forward.

22                      And this is just an example of the

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1 data, but it illustrates why it's relatively  
2 easy to make a decision in this case -- that  
3 if you look at the line, the x-axis here, and  
4 then here is the percent change in the tumor  
5 volume, and this is a decrease -- that  
6 virtually all of the patients had a decrease  
7 in tumor size. So, it was pretty obvious early  
8 on that there was benefit.

9 And the other important part is  
10 that it's not just a response, but a response  
11 that lasts for a significant duration, so a  
12 durable response as well. And the toxicity of  
13 the agent was quite reasonable compared to  
14 other chemotherapeutics, especially that lung  
15 cancer patients may be treated with. So, the  
16 overall risk/benefit is very positive.

17 So, that program has proceeded  
18 quickly, and it is in pivotal trials now,  
19 heading towards approval, hopefully. But,  
20 again, it shows the benefit of focusing on a  
21 patient population, because if we had looked  
22 at all of lung cancer patients, treated

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1 everyone, with benefit only coming to those 10  
2 percent, we would have missed it; we would  
3 have missed that effect in the overall  
4 population.

5 Another interesting project, this  
6 is a slightly different angle, but using human  
7 genetics to define a target for a therapeutic.  
8 This is PCSK9. PCSK9 plays an important role  
9 in LDL metabolism, in that the PCSK9 molecule  
10 is secreted, it binds to the receptor, and if  
11 it does bind to the LDL receptor, the receptor  
12 is degraded. If it doesn't bind, that there is  
13 recycling of the receptor. So, that way, more  
14 cholesterol can be brought into the cell, and  
15 your cholesterol levels will go down.

16 So, there's a patient population  
17 that was defined by Helen Hobbs and her group  
18 at Dallas that was very interesting, a very  
19 small group, of course. But these patients had  
20 low LDL cholesterol. I don't think the low  
21 showed up, but this is a 28 percent decrease.  
22 And in terms of cardiovascular events, they

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1 had about a 90 percent decrease in  
2 cardiovascular events. So, we know that they  
3 were relatively healthy. There were no signs  
4 that this deletion or this mutation was a  
5 problem for the patients. So, long-term  
6 therapy should be okay.

7 We learned a tremendous amount  
8 from these patients in developing this  
9 program, which is an antibody to that target.  
10 And it turns out that, despite the recycling  
11 that occurs, if you expose it to an antibody,  
12 you can stop the PCSK9 from downregulating the  
13 LDL receptor. And therefore, your LDL goes  
14 down. More LDL is taken up, and you can see a  
15 significant reduction in LDL cholesterol in  
16 rodents and primates. And the clinical studies  
17 are ongoing now.

18 But it's a very good example of  
19 using human genetics to find clinical  
20 programs, to find patients that you can look  
21 at, and the development of a therapeutic from  
22 that observation.

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1                   And that occurred relatively  
2 quickly from the first publication, because  
3 that's when the project started, was with  
4 Helen Hobbs and her publication.

5                   So, it's not to say that patient  
6 segmentation and translational medicine is  
7 easy. It's not. Our disease understanding lags  
8 in a number of cases. We just don't know how  
9 to select the patients, how to select the best  
10 patients for benefit by a particular  
11 therapeutic.

12                  We lack a lot of the cell models  
13 and the research models to be able to study  
14 the disease more effectively, and there are  
15 few biomarkers that are actually clinically  
16 validated or available as a surrogate endpoint  
17 that would allow you to use them in clinical  
18 trials for approval process or to move the  
19 programs along more quickly.

20                  So, there's a lot of areas that  
21 need a tremendous amount of work. It is  
22 recognized that that needs to happen, and it's

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1 an opportune time, since we plan to increase  
2 dramatically our focus on translational  
3 medicine, translational research, and we are  
4 very interested in collaboration with groups  
5 in that area.

6 I won't go through all of these  
7 things since I know a number of you are  
8 familiar with it. But there are a number of  
9 challenges for the development of biomarkers  
10 throughout the process.

11 But you need to begin thoughts  
12 about biomarkers right at the beginning of the  
13 research program, so that you have them  
14 available in a validated assay that can be  
15 used clinically when you start the clinical  
16 trials. You have to do that from the very  
17 beginning.

18 You have to then, if that program  
19 progresses into Phase III, you have to have  
20 something that's reproducible in a Phase III  
21 kind of environment. You have to work in  
22 partnership with diagnostics companies to

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1 develop that assay and to have it available if  
2 the program is approved, if the therapeutic is  
3 approved.

4 So, all of these things require a  
5 tremendous amount of collaboration from both  
6 internal and external groups as well as from  
7 health authorities and agencies with this sort  
8 of co-development of a diagnostic along with  
9 patient selection markers.

10 So, a tremendous effort that needs  
11 to be made, and it needs to be made in  
12 collaboration between a number of different  
13 groups to make it successful.

14 So, one of the other points about  
15 collaboration that we want to make, partly  
16 because we were probably not the best  
17 collaborators in the world in the past -- so I  
18 think the focus on biology and improving our  
19 knowledge of biology, on using that biology  
20 across industry, but across academics and  
21 industry is really important. We realize that,  
22 and we want to put a tremendous amount of

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1 effort in developing those partnerships.

2 This is just an example, but  
3 there's many partnerships that we have. We  
4 have thousands, actually, across the world,  
5 looking at various research questions. And  
6 this is an area where we think we need to  
7 collaborate extensively in order to be  
8 successful in terms of translational medicine  
9 and patient biomarkers.

10 So, one example that I wanted to  
11 just show that illustrates some of the changes  
12 in our thinking around intellectual property  
13 partly is an open innovation network. That is  
14 that the institution actually gets access to  
15 our compound files, both in terms of all of  
16 the scientific information there, but also the  
17 compounds themselves, so that they can look  
18 for themselves at what we have in our  
19 portfolio and evaluate whether it would work  
20 in their models and how they might be able to  
21 use it to their benefit but also eventually  
22 produce a useful therapeutic.

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1                   So, this is one example, but  
2                   there's a number of them coming up now.  
3                   There's a new group that we have established  
4                   in Austin to focus on this area of enhancing  
5                   collaboration and sharing information in this  
6                   way that I think will be effective and will  
7                   actually be sharing things like our antibody  
8                   libraries, one of which was published in PNAS  
9                   last year, but a very good antibody library  
10                  that could be effective, could be helpful to a  
11                  number of groups in looking for antibodies to  
12                  novel targets.

13                 And just another example, in this  
14                 case a little bit different-looking for  
15                 targets, but a collaboration with MGH, the  
16                 Broad, and with the Lund University, to look  
17                 for rare genetic variants. So, patients who  
18                 have all of the risk factors for  
19                 cardiovascular disease but don't have it. We  
20                 have all seen them, but we don't know why.

21                 All of the patients who are obese  
22                 and diabetic, and all that just don't have

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1 significant cardiovascular disease, what is it  
2 that is protecting them? We are trying to find  
3 out more about that through human genetic  
4 studies.

5 So, that has just begun in the  
6 last couple of years, but it's illustrative of  
7 a number of different efforts that we have in  
8 human genetics starting up that we want to  
9 pursue in collaboration with institutions  
10 externally.

11 And just one point about biologics  
12 - that biologics, I think, are coming to a new  
13 stage of development where we can do a lot of  
14 manipulation. Not just monoclonal antibodies  
15 or growth factors, but taking those basic  
16 structures and doing a lot of manipulation,  
17 almost what you might have done with small  
18 molecules in the past, so it can create  
19 biologics with biospecificity and a number of  
20 different attributes that would be useful  
21 therapeutically.

22 But we need the biology and the

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1           biologic     expertise     that     targets     the  
2           appropriate patient populations to select and  
3           evaluate in these settings for these to be  
4           useful.

5                        So, finally, I think everyone  
6           agrees that we should be focused on the right  
7           target. We need to do that from the very  
8           beginning, to know as much as we can about  
9           human genetics and human biology, to be able  
10          to do that.

11                      Selecting the right patients,  
12          which has many challenges, but something we  
13          all have to work together to accomplish.  
14          Designing both small molecules and biologics  
15          appropriately for the right patient population  
16          eventually will lead to better, more effective  
17          therapeutics with a better risk/benefit ratio.

18                      So, thanks for your attention.  
19          It's a very large topic. So, it's only a  
20          superficial journey, but I wanted to bring up  
21          some topics that we could discuss as part of  
22          the discussion session.

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1                   And if you have any questions now,  
2                   I'm happy to entertain them as well.

3                   MEMBER RUBENSTEIN: Thanks, Dr.  
4                   Baum. We really appreciate that.

5                   We have time for a few questions.  
6                   Then we will have Dr. Goodman's presentation  
7                   and then maybe a few other questions for the  
8                   two of you.

9                   But if there's some specific  
10                  questions, yes, why don't we start, Bill?

11                  DR. MATTHEW: So, one of the things  
12                  in software development is open software.

13                  DR. BAUM: That's right.

14                  DR. MATTHEW: And you kind of  
15                  alluded to that.

16                  DR. BAUM: Yes.

17                  DR. MATTHEW: I'm just curious as  
18                  to what you think the model might be for drug  
19                  development.

20                  DR. BAUM: Yes. And so, in a  
21                  similar vein, the biology is sort of the  
22                  hardware, the software that we all need to

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1 work with, and that discoveries in that area,  
2 discoveries of new targets and unique biology  
3 is something we can share with academic  
4 institutions, with biotechs, with other  
5 companies, in fact.

6 And then, it is how we reduce that  
7 to practice. Our ability to make small  
8 molecules or biologics to attack these issues  
9 is really where the proprietary part comes in.  
10 So, we're less worried compared to the past  
11 when we were very protective of anything.

12 It's like we used to stamp  
13 everything top secret, but it wasn't. You  
14 know, it wasn't needed to do that, and it kept  
15 us from doing a lot of collaborations and  
16 interacting effectively with many people. So,  
17 that needs to change. It is starting to change  
18 now, and it is something that Michael Dolston,  
19 the head of Research and Development, is very,  
20 very adamant about, that we need to change  
21 that. That's basically the model of open  
22 innovation.

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1                   So, exactly how we do it, there's  
2                   a few different ideas. One is like with  
3                   Washington University sharing the database  
4                   about compounds. There's also something we're  
5                   starting up in Cambridge with the local  
6                   universities to look at actually having some  
7                   dedicated people from the company who would  
8                   form a real close working relationship and  
9                   partnership with the university and that would  
10                  basically function as one, as a way of  
11                  optimizing that interaction and having a  
12                  situation where we both have skin in the game.  
13                  So, there's a real need for the collaboration,  
14                  and both sides see it.

15                 So, it's not just sort of some of  
16                 the typical collaborations we have had in the  
17                 past that really haven't been a huge benefit  
18                 to either one. I think we can do much better  
19                 there.

20                 MEMBER RUBENSTEIN: And are there  
21                 any others?

22                 Gene, yes?

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1                   MEMBER WASHINGTON: First, thanks  
2                   very much for a very interesting and  
3                   informative presentation.

4                   I would like to go back to the  
5                   graphic that you showed regarding what percent  
6                   of overall investments resulted in success.

7                   DR. BAUM: Okay. Yes.

8                   MEMBER WASHINGTON: So, my  
9                   question, though, is looking ahead, projecting  
10                  an optimistic scenario under the new paradigm,  
11                  what might that graphic look like?

12                  DR. BAUM: So, the idea is that,  
13                  since less than 10 percent of our programs  
14                  make it through to a therapeutic, that if you  
15                  could just decrease that by a third, right, or  
16                  increase, or however you look at it, if we  
17                  decrease attribution by a third, that would be  
18                  a tremendous amount of research that could be  
19                  put towards other programs to go faster or to  
20                  look for new targets.

21                  And that 30 percent is a huge  
22                  number, obviously, if you're looking at the

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1 total R&D spent by all of the large pharma  
2 companies, since ours alone is on the order of  
3 \$8 or \$9 billion.

4 So, the amount of research is  
5 tremendous. If we can harness it better and  
6 stop programs sooner, that would suck up all  
7 those resources if they went into Phase III.  
8 So, we think that is definitely doable.

9 We don't think we can get to zero  
10 attrition and we shouldn't, because you want  
11 to bring some things into the clinic that  
12 you're not sure about. You want to take that  
13 risk. But you need to make the decision  
14 relatively sooner to stop something that's  
15 really not in the best interest of the  
16 patients.

17 MEMBER RUBENSTEIN: Steve?

18 MEMBER KATZ: Thank you again.

19 Part of the new paradigm that you  
20 talked about was a focus on rare diseases.

21 DR. BAUM: Yes.

22 MEMBER KATZ: Could you tell us a

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1           little bit about that?

2                     DR. BAUM: Yes.

3                     MEMBER KATZ: I guess that fits in  
4           with your patient segment.

5                     DR. BAUM: Yes.

6                     MEMBER KATZ: But you made it a  
7           point specifically about rare disease.

8                     DR. BAUM: That's right, and I  
9           think there had been some discussion about  
10          this in the past, but I think you've seen real  
11          action now, finally.

12                    So, there is a group that has been  
13          established in Cambridge as well to focus  
14          entirely on rare diseases. And their mandate  
15          is to, for the most part, work  
16          collaboratively. There is an internal group,  
17          but, also, we recognize the need to work with  
18          the academic centers and the people that have  
19          these rare patient populations, since they are  
20          not easy to access, to focus, to help them in  
21          some cases to develop a therapeutic, but also  
22          to look for new opportunities in those for new

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1 targets that might be effective. So, that is a  
2 huge change for Pfizer and a big change in  
3 emphasis towards those less common diseases.

4 And there's a good example just  
5 recently with FoldRX that we acquired. Their  
6 whole focus is in amyloidosis, a very rare  
7 condition initially.

8 So, it is really showing by our  
9 actions that we are very interested in those  
10 areas. We think there's lots of clinical  
11 benefit that we could bring to those patient  
12 populations.

13 MEMBER RUBENSTEIN: I would like,  
14 Dr. Baum, you know, agreeing that Pfizer is a  
15 worldwide company, one of the interesting  
16 things is the way you position these new or  
17 these expanded areas.

18 DR. BAUM: Yes.

19 MEMBER RUBENSTEIN: And I just  
20 wonder, from your point of view, if the  
21 climate in the United States is less positive  
22 than the United Kingdom or other places.

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1           Because it is a thing we wrestle with a great  
2           deal, and if it is so, we need to think about  
3           that in terms of encouraging you to deal with  
4           some of the issues here.

5                       DR. BAUM: Yes.

6                       MEMBER RUBENSTEIN: So, you know,  
7           there's a lot going on in Cambridge, for good  
8           reasons. I just wonder what your thoughts  
9           about that are.

10                      DR. BAUM: Yes. So, I think it  
11           depends on what aspect we're trying to focus  
12           on. So, I think in terms of biology and the  
13           deep knowledge and the innovative science,  
14           that still there's a big emphasis in the U.S.  
15           and Western Europe and other key academic  
16           centers that have that information.

17                      But that is not to say that we are  
18           not interested in working elsewhere. So, our  
19           initial focus will be in those areas, but to  
20           expand to Asia, obviously, is one of the other  
21           greatly expanding areas now for all of us,  
22           that we need to get into more work there,

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1 which we haven't yet. And it probably will  
2 take a bit longer to develop those kinds of  
3 relationships.

4 But we have existing relationships  
5 with some of the institutions in California  
6 and on the East Coast that we want to  
7 optimize. So, that is part of the reason for  
8 their location. But we are interested in  
9 looking at other opportunities. As this  
10 succeeds, we would like to see it go into a  
11 number of different places.

12 MEMBER RUBENSTEIN: Francis?

13 DIRECTOR COLLINS: I want to follow  
14 up a little bit on the question that Bill  
15 asked in terms of the open sourcing of the  
16 enterprise in a way that still protects  
17 intellectual property, but which empowers  
18 people who are doing an increasing amount of  
19 efforts to do high throughput screening for  
20 therapeutic purposes to have access to  
21 molecules that have added value, because they  
22 have already been put into circumstances where

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1           you know a lot about them.

2                       Your model with WashU is very  
3           interesting in that regard, but some of us  
4           might even say, why not really open that up --

5                       DR. BAUM: Right. Yes.

6                       DIRECTOR COLLINS: -- so that  
7           pharmaceutical companies develop relationships  
8           with high throughput screening centers, some  
9           of which NIH now funds as part of the Common  
10          Fund? So that every time a screen gets done  
11          with a target that's potentially relevant to a  
12          rare or common disease, you have a chance of  
13          getting a hit that's already well along the  
14          pathway, and you've saved a lot of money and a  
15          lot of time.

16                      DR. BAUM: Yes.

17                      DIRECTOR COLLINS: We're going to  
18          be running a meeting later this fall to sort  
19          of look at this question of repurposing on a  
20          broader scale.

21                      DR. BAUM: Yes.

22                      DIRECTOR COLLINS: And also, sort

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1 of rescuing, perhaps, compounds that have been  
2 abandoned along the way for various reasons.

3 But maybe as a little  
4 foreshadowing of that conversation, do you see  
5 any barriers towards really opening up that  
6 potential, as long as careful thought is put  
7 into the IP considerations? Because  
8 companies, after all, have already invested a  
9 lot of their resources in developing  
10 information about these compounds.

11 DR. BAUM: Right. But I think what  
12 we also realize is that, if they sit on the  
13 shelf, there's no value, either. So, we may  
14 own it, but nothing good is happening.

15 So, what we need to make sure is  
16 that key parts, the composition of matter and  
17 things like that, are protected. But, then,  
18 beyond that, especially in the cases where we  
19 just don't know what to do, and there's a  
20 number of those cases, we don't know where to  
21 go, that opening it up to a lot of external  
22 sites would make sense.

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1                   And so, I think these are initial  
2                   steps, but that is definitely a possibility  
3                   that we have talked about, and how you would  
4                   make sure that's done in a way so that it's  
5                   just not everything going out in all  
6                   directions and then you lose track of what's  
7                   happened, and negative things can come back to  
8                   you.

9                   So, you just want to get a better  
10                  system, and we don't have it now, of doing  
11                  that follow-up and making sure that we know  
12                  what's going on and how we can best benefit  
13                  from the collaboration, so that we both share  
14                  in that partnership, basically.

15                 So, it's not worked out. We need  
16                 to work on that more, but we are open to that  
17                 idea, and I think it's a good discussion to  
18                 have.

19                 MEMBER RUBENSTEIN: So, let's have  
20                 two more questions. Then we'll ask Dr. Goodman  
21                 to give us his perspective. Then we may have  
22                 time for a few more questions.

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1                   So, first, Tony?

2                   MEMBER FAUCI: Charles, I couldn't  
3 help but think, as you were presenting this, I  
4 agree completely with the concept of fail  
5 early and fast and get out.

6                   DR. BAUM: Yes.

7                   MEMBER FAUCI: When you're talking  
8 about a clinical trial, sometimes that's  
9 pretty obvious. Phase I, if it doesn't happen,  
10 it doesn't happen, if it's toxic. Or if you're  
11 even in a Phase II trial, you have DSMBs  
12 looking at futility, et cetera.

13                  DR. BAUM: Right.

14                  MEMBER FAUCI: But since we're  
15 talking about the potential role of the NIH in  
16 translational research, how do you see in your  
17 own company, when you do research that is  
18 directed at developing something but there's a  
19 lot of other questions that might arise, as we  
20 all know who do basic research, that don't  
21 have anything to do with what your original  
22 intent is?

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1 DR. BAUM: Right.

2 MEMBER FAUCI: It can be a little  
3 dangerous to drop it, because it doesn't go  
4 with your original intent.

5 DR. BAUM: Right.

6 MEMBER FAUCI: How do you see that  
7 integrating into what we're trying to do? I  
8 agree with you completely; when you are  
9 looking at a particular product, fail early,  
10 fail fast. But what about the information that  
11 might come out of a failed product but that  
12 might give you something else two years later?

13 DR. BAUM: Yes, absolutely. I think  
14 that's something we have done very poorly,  
15 actually, and in two ways. One, learning from  
16 those negative clinical trials and getting the  
17 information fed back into research for  
18 ourselves and for others. Why did it fail?  
19 What was the reason? Was it just a bad  
20 compound or there's some other reason?

21 But I think, also, the point that  
22 was mentioned earlier, that I think there are

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1 cases where we'll have compounds that don't  
2 meet the endpoint we were looking for but that  
3 may have clinical utility elsewhere, that we  
4 could open that up to let other people  
5 investigate and find out if that's the case.  
6 But it's not something that we have the  
7 resources to do everything.

8 So, I think those are good cases.  
9 And then there's cases, obviously, where it is  
10 just flat failure, right, and it's not coming  
11 back in any kind of reincarnation. There's no  
12 Lazarus factor for that.

13 So, we can be clear about that  
14 and, I think, talk it through the different  
15 compounds with the scientists. Where was there  
16 a hint of activity or some reason to pursue  
17 it, even though the initial indication was not  
18 the appropriate one?

19 MEMBER RUBENSTEIN: Gail?

20 MEMBER CASSELL: Yes. Francis, I  
21 would say in the not-for-profit Lily TB drug  
22 discovery effort, we give full access to our

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1 entire chemical library. Merck gives limited  
2 access. It's a partnership with NIAID, Lily,  
3 and the Infectious Disease Research Institute  
4 in Seattle, and also Academia Sinica in  
5 Taiwan, which has a library of 2 million  
6 compounds that they also share.

7 We have been able to work out the  
8 IP issues, the blinding of structures, the  
9 release of structures, depending on hits,  
10 quality of hits, and decisions to go forward  
11 or not.

12 So, I would be optimistic that  
13 maybe some of the learning from this  
14 experience since 2007 might be helpful in  
15 terms of trying to establish some of the types  
16 of collaborations I think you're suggesting  
17 could be important for the future.

18 MEMBER RUBENSTEIN: Let's have a  
19 comment from Harold, and then Dr. Goodman.

20 MEMBER VARMUS: Just a very quick  
21 comment about these extended collaborations,  
22 which seem very welcome. I hear of efforts

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1 with academia. When you think about these  
2 extant calibrations, do you think about the  
3 NIH, the government?

4 DR. BAUM: Yes.

5 MEMBER VARMUS: And you think  
6 differently about that?

7 DR. BAUM: So, to be honest, I  
8 think there's a lot of history of Pfizer  
9 avoiding it. Well, it's obvious.

10 But now I think that's totally  
11 different, and viewing it, basically, as an  
12 academic collaboration, you know, other  
13 institutions. So, I think it is definitely  
14 something that would make a lot of sense in  
15 collaboration with the clinical --

16 MEMBER RUBENSTEIN: It is certainly  
17 inherent to the TMAP concept, Harold.

18 MEMBER VARMUS: Yes, I know, and I  
19 have an eye on that, because it is really a  
20 different set of collaborators.

21 MEMBER RUBENSTEIN: Right.

22 DR. BAUM: Yes.

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1                   MEMBER RUBENSTEIN: So, I think it  
2                   is really an important question.

3                   MEMBER KATZ: But certainly Pfizer  
4                   has -- let me just add one point -- Pfizer  
5                   actually played a leadership role in a  
6                   public/private partnership for a pre-  
7                   competitive identification of surrogate  
8                   markers in the osteoarthritis initiative.

9                   DR. BAUM: Yes.

10                  MEMBER KATZ: And it's because of  
11                  Pfizer that many companies came along without  
12                  any benefit at all in an initiative that's  
13                  really a true partnership.

14                  DR. BAUM: So, we are trying to  
15                  expand that to a number of other areas. I  
16                  think, with your help, we can do that.

17                  MEMBER RUBENSTEIN: Thanks, Dr.  
18                  Baum.

19                  DR. BAUM: Thank you.

20                  MEMBER RUBENSTEIN: So, of course,  
21                  there is a role of the FDA, together with NIH  
22                  and other government bodies, that is

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1 critically important. We are privileged today  
2 to have Dr. Jesse Goodman, Chief Scientist,  
3 Deputy Commissioner for Science and Public  
4 Health at the U.S. FDA Administration.

5 Jesse?

6 DR. GOODMAN: Okay. I don't think I  
7 have any slides. Okay.

8 Actually, I sent Amy an email. Amy  
9 promised me I wasn't giving a talk, because I  
10 only was able to free up time to do this as of  
11 yesterday, but I will try my best to say  
12 something helpful to you.

13 I'm really very, very excited to  
14 see what's going on here and see NIH and our  
15 colleagues in academia and industry looking at  
16 this development process.

17 And maybe I will just give a few  
18 broad comments first and then talk a little  
19 bit about why the timing is good with our  
20 whole regulatory science initiative at FDA.

21 I would also like to mention  
22 something that Tony Fauci and I have spent a

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1 lot of time working on, because I think there  
2 are many lessons and models there, which is,  
3 what can we do to enhance development of  
4 products needed for unmet public health needs  
5 and for national defense? And I think the  
6 models we have put together for how  
7 government, industry, NIH, FDA can work  
8 together there innovatively are relevant to  
9 many of the things we are talking about here.

10 So, I thought I would first just  
11 react with a few things that come to mind from  
12 hearing this talk and sort of the big-picture  
13 messages and as somebody who has seen this  
14 from a number of ends.

15 Oh, I also want to say that I  
16 have, obviously, colleagues here previously  
17 who are at Minnesota, at Penn, and places I've  
18 been. So to thank them for all their support  
19 over time.

20 But, anyhow, I think the really  
21 big-picture things that I would like to  
22 mention, so I don't forget them, are that I

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1 absolutely think that product development  
2 needs to be transformed. I think that is  
3 totally against the grain for industry, for  
4 FDA, for NIH, for everyone.

5 There is, sort of, nobody who  
6 wants to own that, and everybody will look at  
7 their piece and try to improve it, and they  
8 will call that transformation, but people  
9 really aren't stepping back and looking at  
10 this.

11 Now, in some cases the technology,  
12 like genomics and personalized medicine, will  
13 drive things that are truly transformative.  
14 But I think unless we -- and again, we tried  
15 to do this in the countermeasure initiative --  
16 unless we really ask ourselves hard questions  
17 and say, should we be doing this completely  
18 differently, we're going to miss some  
19 opportunities.

20 Now, as my lab chief used to say  
21 to me, you know, it's fine for me to say  
22 something like this. It's a lot harder to do

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1 it. And he said, you know, "If this was easy,  
2 everyone would be doing it," you know, about  
3 the work we were doing in the lab. And I said,  
4 "Well, it seems like everybody is doing it."  
5 But that didn't go very far.

6 In terms of big principles that  
7 really can be transformative of how we think  
8 about these things, I think one is we really  
9 need to focus not only on saying we have to do  
10 things completely differently, but on the  
11 outcome. Okay? So what is it at all times  
12 we're trying to achieve? Is it a disease? What  
13 would be the ideal outcome of an intervention  
14 in that disease? Not letting a drug or a  
15 development process drive the outcome, but  
16 having the outcome start to drive that  
17 process. It sounds very general, but I think  
18 it's not generally an operational principle.

19 In terms of FDA, I think the  
20 biggest message here is that we would like, to  
21 the ability of our resources, both human and  
22 scientific, and our capacities, to be engaged

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1 in these efforts throughout, both early on and  
2 during the product development and evaluation  
3 process.

4 I think that what has to happen is  
5 a bringing together of two different cultures.  
6 There is a culture that people like to think  
7 of as a culture of innovation and discovery,  
8 although I would argue that much discovery is  
9 not necessarily innovative. It's discovery,  
10 and it's incremental.

11 But there is sort of a culture of  
12 discovery, and then there is a culture of  
13 process. FDA and industry often focus pretty  
14 well on that process discovery, that process  
15 piece. Academia and basic scientists often  
16 focus on this discovery and innovation piece.

17 But I think these are viewed as  
18 completely opposite cultures and in collision.  
19 I think the real challenge is to start to  
20 understand how they could be mutually-  
21 beneficial.

22 If you're lost all the time in

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1           your process, which is the world I live in a  
2           lot of the time, you really risk losing  
3           innovation and, in fact, stifling it.

4                       On the other hand, if you pay no  
5           attention to process or validation of your  
6           tools, or things like that, your discoveries  
7           really end up having much less value or  
8           certainty that they would have, which is where  
9           FDA steps in. So, I think, involve us early  
10          throughout.

11                      And then, to build on the theme  
12          that I just heard about, information -- think  
13          about the internet -- information is totally  
14          being transformed. I mean, not just the  
15          internet, but Twitter and all information.  
16          It's now an artificial situation if  
17          information is protected or in one little  
18          place. Even the intelligence agencies can  
19          barely manage to do that anymore.

20                      So, again, we can either fight  
21          that, which inherently innovation tries to  
22          protect its intellectual property, and that

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1 helps drive the economics of innovation or, as  
2 I just heard Gail and Dr. Baum say -- oh, not  
3 Dr. Baum -- saying that we really need to  
4 think about ways of using the information. We  
5 have more, not less. Because, otherwise, it  
6 will happen anyhow. So this transparency.

7 And as an example of something  
8 that people have suggested in the drug  
9 discovery process, we have seen some sharing  
10 of unused or compounds for repurposing, as was  
11 mentioned. That's great.

12 But, also, we have heard about, at  
13 what point could you make data public and  
14 available for other people to analyze, other  
15 than the individual NIH scientist or  
16 innovator? So, not just the results, but the  
17 data; that could really transform how we do  
18 things.

19 Now a few comments about FDA and  
20 its role. What people often don't appreciate  
21 is that we are seeing not just single  
22 products, but multiple products across

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1 multiple discovery and development efforts. So  
2 that we do have a unique place where we can  
3 learn from failure and learn from success and,  
4 in ways that protect people's intellectual  
5 property, share that information. So, I think  
6 this is a way we can help catalyze success in  
7 that area.

8 Now, if translational medicine is  
9 a huge gap that Dr. Zerhouni, Dr. Collins, all  
10 of you have identified -- which is going from  
11 the molecule to the patient, essentially --  
12 what we're calling regulatory science, or  
13 going from the molecule and patient to a  
14 product that can help people and the  
15 evaluation methods that we need and the models  
16 and tools, has received even less attention.  
17 Okay?

18 So, what we are arguing for -- and  
19 this is where I will bring up the analogy of  
20 the countermeasure initiative -- is for FDA to  
21 have the capacity to be engaged early in this  
22 development process. In the countermeasure

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1 initiative, for example, when HHS determines a  
2 serious public health threat or a priority  
3 need for a countermeasure, when we've looked  
4 at best practices and what has succeeded, what  
5 we have seen is when we are working closely  
6 together with our colleagues at NIH and  
7 industry from a very early point, the  
8 enterprise is much more likely to be  
9 successful.

10 What we plan to put in place as  
11 part of this initiative, which is being  
12 resourced significantly because it requires  
13 that on our end, is to look early on -- and  
14 again, companies do this to some degree -- and  
15 say, to go from this concept, to meet this  
16 public health outcome, what are the things,  
17 what are the gaps in our scientific knowledge  
18 base that will occur along the way?

19 It could be something as simple as  
20 an assay for the potency of a new vaccine. For  
21 stem cells, another promising area could be,  
22 how do we know that the stem cell we made

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1 three months ago and the cell we make next  
2 year are going to be the same? And that's an  
3 area where we've seen many, many problems in  
4 development, where people can get something to  
5 work in a mouse or to have promising results,  
6 and then, as this is brought into a true  
7 development process, they're not sure they're  
8 making the same product or can't reproduce the  
9 results.

10 So this gets to the tools, the  
11 assays, the measures, things that certainly  
12 academia doesn't intrinsically think about in  
13 development. And frankly, industry thinks  
14 about them in development, but thinks about  
15 them generally in a one-off way. I have my  
16 target for getting to this point in our  
17 clinical development program by this date. How  
18 do I deal with this now? Sometimes that leads  
19 to innovation, but often that leads to pretty  
20 conservative approaches of sort of do  
21 everything. So I think we can really help by  
22 doing that. I think that's really the major

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1 lesson.

2 Then the other part is  
3 collaboration, and new models of  
4 collaboration, and in some cases financing.  
5 So, in the private sector, we are hearing you  
6 talk about multiple companies getting together  
7 in certain ways. As we're trying to deal with  
8 these public health products, where the  
9 financial incentives are not there or are  
10 uncertain, we're trying to find novel ways to  
11 bring multiple people together, to get  
12 products that might have uses not just in  
13 public health but more generally, and to make  
14 it so that the enterprise is win/win for  
15 everyone. So that the government and the word  
16 "ability" can be used in the same sentence  
17 through processes that are much more  
18 innovative.

19 I think those are actually the  
20 major points I wanted to make. You know, a few  
21 other things is that -- and again, this was  
22 alluded to, and I know that your group and,

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1           also, the IOM are looking at this. But we  
2           really see at FDA the challenges around  
3           clinical trials and clinical development. I  
4           think that is very worthy of a lot of  
5           attention.

6                       On the FDA end, as Chief  
7           Scientist, what we would like to do is really  
8           change the way we do clinical trials. The  
9           clinical trials should focus on population and  
10          disease subsets to the extent possible. But  
11          where we even don't know that going in, they  
12          should be adaptable, flexible to capture that  
13          data during the clinical development process.

14                      One of our big emphases or  
15          scientific emphasis areas -- and we're working  
16          on this with colleagues at NIH, including NCI  
17          -- is, how do we start having data systems  
18          that let us bring together data, for example,  
19          from multiple clinical trials, from multiple  
20          kinds of intervention, data on natural history  
21          of disease, both biologic and clinical data,  
22          and then, hopefully, at some point data from

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1 the healthcare system?

2 Because I would estimate that  
3 right now we are not probably learning from 90  
4 percent of the data that we collect. We are  
5 learning from it in a very narrow area of the  
6 clinical trial for drug or vaccine or product  
7 A for disease B, but we're not using that data  
8 or comparing it with other studies and  
9 products, learning about natural history of  
10 disease, or combining it with more  
11 generalizable biologic or healthcare  
12 information.

13 So that's why --

14 MEMBER RUBENSTEIN: Dr. Goodman,  
15 maybe you'll finish so we have time for a few  
16 questions?

17 DR. GOODMAN: Oh, yes. I will stop  
18 there. I will stop.

19 MEMBER RUBENSTEIN: Are you sure?

20 DR. GOODMAN: Yes. Yes.

21 So, again, we want to work with  
22 you on intent and involvement. I'm totally

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1 convinced that the current models of  
2 development aren't working. They're not.  
3 Tweaking will help it, but we really need to  
4 do things differently, both at the very basic  
5 discovery end, where we need to encourage more  
6 creativity, and at our end, where we really  
7 need to develop better evaluation tools, so  
8 that we aren't going on and on trying to  
9 detect small benefits in very heterogenous  
10 populations.

11 MEMBER RUBENSTEIN: Thank you. I  
12 really appreciate your perspective. I just  
13 want to be sure we have enough time to ask you  
14 questions.

15 DR. GOODMAN: Sure.

16 MEMBER RUBENSTEIN: So, Steve?

17 MEMBER KATZ: Thanks, Jesse.

18 In terms of incorporation of new  
19 paradigms, could you tell us how the FDA is  
20 looking at patient-reported outcomes? We  
21 talked a little bit about that during the  
22 break in terms of assessment of new drugs, new

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1 interventions.

2 DR. GOODMAN: Yes. I think that we  
3 need to look at clinical study outcomes in  
4 general in a very systematic way and that  
5 patient-reported outcomes can be a really  
6 important part of that. We have been working  
7 with you and various consortia on this area.

8 So, obviously, the part of the  
9 response to a therapy that is really most, and  
10 sometimes far more, accurate than our biologic  
11 measures is how the patient feels, how the  
12 patient reports their functional status.

13 This is very tricky to validate  
14 and very easy to go wrong with. But we are  
15 very enthusiastic about this. I know measures  
16 have been developed that are pretty well  
17 validated in areas like asthma that, I think,  
18 in the long-run could provide outcomes in  
19 clinical studies -- and not just in clinical  
20 studies, but in healthcare interventions --  
21 that tell us what really works and what  
22 doesn't. You know, it doesn't matter if your

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1 MRI shows this or that if you don't feel  
2 better. So we are very enthusiastic about  
3 that.

4 But I want to extend this to a  
5 broader concept of outcomes. I think the  
6 patient has been missing from the outcomes.  
7 And so, these are incredibly important  
8 efforts.

9 But I think, to get back to my  
10 point about meaningful benefit, you know, we  
11 really need to look at that more generally. We  
12 need better surrogate outcomes, more use of  
13 accelerated approval mechanisms for serious  
14 diseases, which is now hampered by the lack of  
15 surrogate outcomes. But then we need to follow  
16 those up and be sure we have outcomes that  
17 really are about benefit.

18 And frankly, I think companies are  
19 starting to look at things this way. But if a  
20 drug or another intervention do not appear to  
21 have much benefit over existing therapies,  
22 unless there's some other significant thing

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1           that's going to make patients' lives better, I  
2           think we shouldn't be spending a lot of energy  
3           on it.

4                   MEMBER RUBENSTEIN: Tony, did you  
5           want to comment on some of your interactions?

6                   MEMBER FAUCI: Actually, as Jesse  
7           alluded to, we have been working on this now  
8           for it seems like months, but it's probably  
9           close to two years, on this in regard to some  
10          of the issues of emerging diseases and things.  
11          So, we already have a big head start. The  
12          question is, I think we have a long way to go,  
13          as Jesse pointed out.

14                   MEMBER RUBENSTEIN: Yes, Gail?

15                   MEMBER CASSELL: Jesse, a number of  
16          recent reports have emphasized the need for  
17          the science base at FDA to be strengthened in  
18          order to catch up with drug discovery and drug  
19          development, and suggesting that maybe there  
20          should be more interaction between FDA and  
21          academic health centers in terms of active  
22          collaboration.

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1                   And I wondered if you could  
2                   comment on this and, as the Chief Scientific  
3                   Officer, how you see this changing over the  
4                   next couple of years in order to take  
5                   advantage of the development of new paradigms  
6                   within NIH and industry?

7                   DR. GOODMAN: Well, I think that  
8                   there are two major components or more to what  
9                   we need to do at FDA. You know, right now --  
10                  and I'm always struck by this as I work with  
11                  all the partner agencies very closely, like  
12                  NIH and CDC -- FDA, you know, it's said all  
13                  the time that FDA, for being responsible for  
14                  overseeing a quarter of the country's economy,  
15                  being in a world of zero-tolerance for all the  
16                  challenges that we face, whether it's  
17                  salmonella in eggs or getting flu vaccine in  
18                  time, these are all scientific issues with  
19                  science at their base.

20                  Every decision we make is a  
21                  scientific decision. Even enforcement  
22                  decisions should be based on science. And the

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1 quality of FDA's decisions is based on its  
2 scientific capacity and excellence.

3 So we have a big rebuilding and  
4 building job to do. FDA internally needs more  
5 scientific capacity. You know, when I came to  
6 FDA from academia, I said, gee, I deal with a  
7 dozen -- I went from running infectious  
8 disease, including on a transplant unit at a  
9 wonderful transplant center, to dealing with  
10 some of these daily public health issues, and  
11 all of them were much more complicated and  
12 challenging and had equal or more at stake  
13 than the complicated decisions we make in the  
14 academic healthcare arena.

15 So, we need really good people. We  
16 need to make it an attractive, independent,  
17 proud agency.

18 And I was delighted to see a *New*  
19 *Yorker* column about a month ago that was going  
20 on and on about all the broken regulatory  
21 things. It actually said there is this success  
22 at FDA, because people see themselves as

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1 scientists and as protecting public health.

2 So, we need to rebuild internally,  
3 but we also, like everybody in this room,  
4 recognize that we want to and need to  
5 collaborate more. We want to really build this  
6 relationship with NIH, and Peggy and I are  
7 very excited about the work we're going to do  
8 with NIH on this Council, how we have worked  
9 with Amy in putting out a Request for  
10 Applications to try to get the academic  
11 community interested in the kind of applied  
12 regulatory science we need to have better  
13 methods and evaluation tools.

14 And we would also love to, and we  
15 have proposed starting, a network of Centers  
16 of Excellence in regulatory science where we  
17 could try to build training and capacity in  
18 academia that, I think, would also help NIH in  
19 the long-run gets its job done, because, you  
20 know, we just all have different perspectives  
21 and things we can bring to the table.

22 MEMBER RUBENSTEIN: Other questions

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1 for Jesse or Dr. Baum?

2 (No response.)

3 If not, thank you very much.

4 DR. GOODMAN: You're welcome.

5 MEMBER RUBENSTEIN: That was very  
6 helpful.

7 So, we have our first panel  
8 discussion, as I mentioned. I want to thank  
9 the participants for coming today on  
10 relatively short notice.

11 And we have two moderators who are  
12 going to run the program, Steve Katz and Bill  
13 Brody from the SMRB.

14 Would you like to introduce the  
15 members, Steve or Bill, or however you would  
16 like to do that, and then moderate the  
17 session?

18 MEMBER BRODY: I think everybody  
19 has a list of their bios, and in the interest  
20 of time, Steve and I decided we probably would  
21 just jump right into the discussion.

22 I want to again thank you for

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1 coming. I know many of you have really  
2 rearranged your schedule to be here.

3 I thought what we would do -- and  
4 Steve and I as moderators, neither of us is  
5 described as moderates.

6 (Laughter.)

7 But our role is simply to make  
8 sure that everybody has an opportunity to  
9 weigh in.

10 I think, clearly, what we have  
11 heard is that business as usual for the  
12 pharmaceutical industry and drug development  
13 is probably not the right model, and there's a  
14 new paradigm. You heard some excellent  
15 thoughts from Dr. Baum and Dr. Goodman about  
16 this, and there will be more discussion.

17 What I think we would like to do  
18 is just to start and kind of go through the  
19 questions and let each of you comment first.  
20 Then we will sort of work it as-is, as it  
21 comes.

22 But I would like to ask each of

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1           you to comment very briefly, since we've got a  
2           large number of you. What do you think is the  
3           new paradigm? Or how do you react to what's  
4           been talked about?

5                       And I should point out we've got  
6           everybody here from Wall Street to basic  
7           science in academia, to public policy  
8           advocates and patient advocates.

9                       So I'm curious to hear what your  
10          thoughts are about how to fix the system or  
11          change the system that everybody, I think,  
12          agrees is in need of dramatic reform.

13                      Shall we start with Dr. Berger,  
14          Wall Street, first?

15                      MR. BERGER: I'm not a doctor.

16                      (Laughter.)

17                      This has been very illuminating  
18          for me, and I'm delighted to see that there's  
19          so much interest here at the NIH, which I  
20          respect a great, great deal.

21                      My background is in underwriting  
22          biotech companies and then helping people

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1 invest in biotech companies large pools of  
2 capital, and now working on Boards and with  
3 the business development. So I feel very much  
4 in the mix here.

5 What's happened in the real world,  
6 as much as I enjoy understanding the science,  
7 industry has already adapted to the changing  
8 reality. One of the paradigms I see is  
9 something that Bristol-Myers has taken up, and  
10 the early beginnings of the biotech industry,  
11 which is where I started following this  
12 industry in the eighties.

13 The companies were what some  
14 investors call specialty pharma companies, and  
15 they chose to use translational research not  
16 because of its elegant beauty and scientific  
17 merit, but because it's a better business  
18 model.

19 To give an example, in the  
20 multiple sclerosis business, why did Biogen  
21 succeed so well? They chose a distinct patient  
22 population that had a large unmet medical need

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1 where the needs for a perfectly-safe drug were  
2 much less, that a relative modest improvement  
3 would be dramatically appreciated by the  
4 patients, by the society, and would be  
5 rewarded to the shareholders.

6 And this is what has made the  
7 small company biotechnology model successful,  
8 both commercially and scientifically. That has  
9 funded a large industry that has gone from  
10 almost no biologics to approximately \$40  
11 billion in biologics, and still growing at 20  
12 percent. So, I think that has already  
13 happened.

14 Some of the bigger biotech  
15 companies, such as Amgen and others, Gilead,  
16 have experienced dramatically decelerated  
17 growth as they've gotten to larger sizes.

18 A couple of light-bulb moments for  
19 me that came up was listening to Dr. Goodman.  
20 The difference between a translational trial  
21 that's exciting and successful and  
22 illuminating and a registrational trial that

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1 creates a company or allows you to develop a  
2 business model are entirely different animals.

3 What I heard Dr. Fauci talk about,  
4 and Dr. Collins, is creating an alliance or a  
5 point of tangency between the NIH and the FDA,  
6 so that the difference between a translational  
7 trial that's a great publication and a great  
8 clinical trial that gets you onto the market  
9 as early as possible is a real positive for me  
10 and for other investors to see that  
11 harmonization.

12 MEMBER KATZ: Thank you.

13 Dr. Duncan?

14 DR. DUNCAN: Ken Duncan. I'm a  
15 Senior Program Officer with the Bill and  
16 Melinda Gates Foundation.

17 I would just like to make a few  
18 comments relative to our position. We are  
19 investing in neglected diseases, so diseases  
20 for which there is clearly no threshold  
21 market, and that's why there are no solutions  
22 in developing countries.

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1                   And we have actually invested in a  
2                   relatively small number of therapeutic areas,  
3                   but we do address issues like malaria, TB,  
4                   some of the neglected diseases, diarrhea.  
5                   That's pretty much our portfolio.

6                   And that touches on both the  
7                   really immediate and urgent issues, which are  
8                   own drug resistance, where existing therapies  
9                   are failing. So, things like arylthromycin  
10                  resistance in malaria is the sort of thing  
11                  that keeps us awake at night, but also XDR-TB  
12                  and the complete failure to be able to treat  
13                  TB patients today in some areas.

14                  But we also focus on the longer-  
15                  term and some of the more transformational  
16                  types of medicines. So, with our malaria  
17                  eradication agenda, we then stop to think  
18                  about, how do you eliminate *P. vivax* and just  
19                  treating acute disease. With TB, we have to  
20                  think about how we shorten the course of  
21                  therapy.

22                  So, it is a bit of a balance

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1           between different things. And that brings us  
2           into very close proximity with a lot of folks  
3           at NIH and other funding agencies' funds. We  
4           try to look for gaps where we can use our  
5           funding in a more catalytic sense to do things  
6           which other funders don't do, but we also try  
7           to look in partnerships.

8                       So, some of the things that  
9           resonated with me, and which I would say are  
10          really critical, are integrating efforts much  
11          better, having the funders aligned. So funders  
12          like NIH, the Foundation, and that's both the  
13          extramural funding, intramural funding, and  
14          also bring in the pharma industry together.  
15          So, the only way we will really make serious  
16          progress in the neglected disease space is if  
17          everybody works in a much more cohesive and  
18          much more coherent way than the current sort  
19          of very disperse ways that things happen at  
20          the moment, which are both inefficient and  
21          unlikely to get us the products that we really  
22          require.

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1                   So, building multidisciplinary  
2 teams all the way through from early discovery  
3 right through to the clinic is really  
4 important. At the moment, there's an awful lot  
5 of handoffs and a lot of things which are done  
6 imperfectly. When products are getting  
7 developed, we have to actually start to go  
8 back a step and often redo things.

9                   We work through grantees, and our  
10 major ones are some of the product development  
11 partnerships. And they have an opportunity, I  
12 think, to really work much more closely with  
13 NIH.

14                  And I was really struck with the  
15 discussion around the Clinical Center this  
16 morning, as to how little we are actually  
17 doing in that space. A lot of people, I think,  
18 just don't realize a lot of what the  
19 capabilities are. We have accessed this to a  
20 certain extent, but not really as much as we  
21 could do.

22                  And there are areas, I'm sure,

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1 where some of that type of research and  
2 funding could be used in a way where the  
3 Foundation wouldn't necessarily want to fund  
4 things and really to expand the number of  
5 things that we're doing.

6 Because we also face the whole  
7 attrition area. We know that we don't have  
8 that many shots on goal. We know that,  
9 although we're bringing a number of products  
10 through, we're going to lose a lot of these at  
11 some stage.

12 And very often, choices are made  
13 at a very early stage, and that is what you  
14 are really faced with moving right away  
15 through the pipeline. Instead, it would be  
16 much more productive if we were to take many  
17 more molecules through into human trials and  
18 get some early clinical data and make the best  
19 choices from those molecules for what things  
20 to really move forward. We are often faced  
21 with just making choices based on animal data.

22 And what else? The issue around

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1 pre-competitive areas is really critical to  
2 us. It is a constant frustration to me to see  
3 how much is done over and over time and time  
4 again because information isn't in the public  
5 domain. And so, trying to build the tools to  
6 allow researchers to put things in the public  
7 domain could be a real useful role.

8 But, also, to try to encourage  
9 people to engage in the public domain in ways  
10 in which everybody can then be working on  
11 molecules, so we have a chance of success,  
12 instead of everybody having their own little  
13 collection of molecules which they will screen  
14 over and over again.

15 And what comes along with that is  
16 repurposing molecules. We have tried really  
17 hard to work with pharma companies to look for  
18 ways of taking molecules that have been really  
19 advanced for one indication and turning them  
20 over to one of our indications. I think there  
21 can be a lot more integration in that in the  
22 anti-infective space.

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1                   And just two final things to  
2                   finish on. One is combination studies. This is  
3                   a real critical issue for us, where we may  
4                   want to take some combination therapies  
5                   through into the Phase III clinical trials.

6                   There's a major effort in the TB  
7                   world at the moment to look at this. There's  
8                   an initiative called CPTR or Critical Path to  
9                   TB Regime Development. That is being done very  
10                  closely with the FDA, but it is basically  
11                  making the recognition that, if we are going  
12                  to get a better new combination TB therapy,  
13                  the way to do that is to test the combinations  
14                  upfront and not test individual products and  
15                  then do replacements.

16                 Then the final point, just to  
17                 touch on this, is the biomarkers area is also  
18                 very important to us. I think that's something  
19                 -- we can't invest that much in biomarkers,  
20                 but it's a really important issue that we  
21                 recognize all the way through the projects  
22                 that we do. And trying to build ways to build

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1 on the networks of biomarker researchers at  
2 NIH would really help the Foundation  
3 tremendously.

4 So, I'll stop there.

5 MEMBER KATZ: Thank you very much.

6 Dr. FitzGerald?

7 DR. FITZGERALD: Thanks, Steve.

8 Well, I think this is a very  
9 timely topic for consideration. To come back  
10 to your original question, my thoughts in  
11 terms of where the future model will be is to  
12 move towards a more modular approach to drug  
13 discovery and development.

14 Given the highly heterogenous  
15 skill sets that are necessary to take a basic  
16 discovery through to an approved drug, it is  
17 no surprise that the best people in the world  
18 at those various components do not reside  
19 within a single company, a single university,  
20 or, indeed, a single country.

21 So, I think the promise and the  
22 potential of the future is that we will move

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1 to a more plastic paradigm of, if you will,  
2 shifting coalitions of the willing around  
3 particular challenges, with modules being  
4 drawn from conventional pharmaceutical  
5 companies, biotech, and the academic sector  
6 across geographies.

7 I think we have nice examples of  
8 how that can work, actually, from the  
9 altruistic sector, where, driven by both  
10 altruism and perhaps the prospect of not  
11 earning much money, people have been willing  
12 to collapse the very outmoded structures of  
13 intellectual property that restrain the  
14 interactions across those sectors presently.  
15 So, I think that is really the promise.

16 Then, of course, a major role for  
17 the NIH is to empower and develop the  
18 capability within the academic sector to be  
19 able to play an appropriate role within such a  
20 modular approach to discovery and development.

21 MEMBER KATZ: Of course, one of the  
22 questions is going to be how to address some

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1 of these challenges and catalyze moving  
2 forward. We will come back to that as the  
3 panel continues.

4 Eric Perakslis.

5 DR. PERAKSLIS: Thank you. Hi.

6 As an informaticist and an R&D CIO  
7 at J&J, the first thing that came to mind is I  
8 was really excited to hear the talk about open  
9 source. I think we have to be tenacious about  
10 this. This is really a big opportunity.  
11 There's a lot of things that we should be  
12 sharing.

13 In fact, we will be back in a few  
14 weeks. Barbara Mittleman is hosting us to look  
15 at some of the stuff that we would like to put  
16 out in the public as a company.

17 Similarly, I think the idea of  
18 biology getting more and more pre-competitive,  
19 I do think it's the right way to go. I think a  
20 lot of companies are taking this move  
21 themselves. And what IMI is trying to do,  
22 although they're hitting some obstacles in

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1 Europe, I think there's some interesting  
2 notions there about drug targets possibly  
3 being pre-competitive, in many ways being pre-  
4 competitive. It's something that is important  
5 to think about.

6 We're also very interested in  
7 biomarkers. I spend a lot of time working on  
8 them.

9 I think we also have to be open,  
10 and we are thinking about what may help NIH to  
11 meet some of the challenges there. We have the  
12 risk of subsetting down to extremely expensive  
13 therapeutics that work on a very small portion  
14 of the population, having to co-develop your  
15 diagnostic and your therapeutic at the same  
16 time. It's not a reason not to do it, it is  
17 just it is something to think about.

18 I like the example of the rare  
19 diseases, especially about, you know, there is  
20 something really fundamentally interesting in  
21 this rare disease biologically that may be  
22 applicable back into a larger biological

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1           setting. So, I think that's really, really  
2           important in making it meaningful.

3                     You know, another thing I say  
4           interesting about this compound repurposing --  
5           I've done a lot of science and technology of  
6           the literature. The interesting thing about  
7           the negative data is you can almost always  
8           believe it.

9                     (Laughter.)

10                    If someone ran a study and the  
11           drug didn't work and they published it,  
12           really, if the model was good, you've got a  
13           lot of biology there. There all the types of  
14           ways you can look at literature and find out  
15           that, well, if this biology is good, it could  
16           cure 20 different things. Well, maybe it  
17           could, and maybe there's some evidence for  
18           some of those statements. But if you mine the  
19           literature, a lot of the negative data is  
20           extremely powerful. So we shouldn't discard  
21           the trial that didn't work. We should be  
22           trying to learn from that.

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1 Thank you.

2 MEMBER KATZ: Thank you.

3 Ms. Selig?

4 MS. SELIG: Thank you. I appreciate  
5 being here.

6 I'm going to give a little bit of  
7 the perspective of the nonprofit venture  
8 philanthropy trying to fill the gap in sort of  
9 the real-world model.

10 The Melanoma Research Alliance is  
11 very new. We are just finishing our third year  
12 and have sort of been incubated in the image  
13 of FasterCures and the Milken Institute. We  
14 have founders who have significant resource  
15 and incredible passion.

16 And they took a look at the  
17 existing paradigm for delivering outcomes for  
18 patients and felt that it was sorely lacking  
19 and wanted to do something about it. So we  
20 were founded, and what we do every day is look  
21 for the best translational research that we  
22 can find and fund worldwide.

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1                   And we don't care about  
2 intellectual property. All we care about is  
3 funding the most promising studies.

4                   And in doing that, we have become  
5 the largest private funder of melanoma  
6 research in this country, having funded about  
7 \$22 million in three years to 50 projects.

8                   So, a couple of things that I was  
9 struck by, and I have a lot of synergy in what  
10 I was thinking with my colleague from the  
11 Gates Foundation. I think that, from my  
12 perspective, and I'm not a scientist, but just  
13 sitting in this incredible place, this is a  
14 time of amazing opportunity, finally, for  
15 melanoma.

16                  So, what we would like to do is  
17 work with the NIH, with the NCI, with the FDA,  
18 with industry, with anybody out there to say,  
19 how can we accelerate the progress that maybe  
20 is finally starting to happen?

21                  One of the things that we have  
22 done in our latest Request for Proposals -- we

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1 generally fund academic institutions and  
2 individuals and teams -- but we have gone out  
3 to say we want to leverage the dollars that we  
4 can put on the table against what we might  
5 encourage industry to do working with these  
6 academic investigators.

7 So a novel kind of partnership  
8 award that we want to fund -- and again,  
9 because we don't care about intellectual  
10 property for ourselves, we really want to  
11 encourage people to just get there faster.

12 And the other point that was made  
13 -- and we have begun a really good dialog with  
14 FDA, and we welcome the opportunity to work  
15 with NIH and NCI -- is this issue of  
16 combinatorial therapies and how do we  
17 accelerate progress, especially when you have  
18 compounds that are in multiple companies. And  
19 obviously you have a desire, which we totally  
20 understand from the market perspective, to  
21 bring something to market as an individual  
22 agent, especially in a field where there's

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1           been virtually nothing for decades.

2                       But at the same time, we know that  
3           it's probably not going to be one agent that  
4           is going to be the answer for these patients.  
5           So, how do we encourage companies to work  
6           together? And are there things that the NIH  
7           can do, that the FDA can do, that we can do to  
8           break down those barriers, so that it is not a  
9           matter of a completely sequential process? But  
10          are there some things that we can do in  
11          parallel process to accelerate this?

12                     And I'll stop there, but I have  
13          some other thoughts for later.

14                     MEMBER KATZ: Thanks very much.

15                     Mary Woolley?

16                     MS. WOOLLEY: Thank you, Steve and  
17          everybody. I must say it's a delight to be  
18          here with people who aren't moderates, who are  
19          passionate about and driven to make sure that  
20          research accomplishes its promise for health.  
21          I think that, in fact, exactly encapsulates  
22          what the American public wants.

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1                   The points I thought I would make  
2                   are more at the 30,000-foot level around your  
3                   question for thought here about, what do we  
4                   need to catalyze, implement, and sustain any  
5                   new paradigm? Ultimately, what we need is the  
6                   support of the American public and its elected  
7                   officials and other policymakers.

8                   We need that support so the  
9                   resources are there and a positive policy  
10                  environment is there. And we're only going to  
11                  get it by engaging the American public every  
12                  step of the way.

13                  I think you heard perfectly well  
14                  from Wendy about the value and the  
15                  intelligence that the private sector patient  
16                  groups, the volunteers, can add to the  
17                  process. And that's entirely consistent with  
18                  what the American public is saying through  
19                  public opinion polls, which you may know we  
20                  commission on a regular basis. So, they want  
21                  to see more public participation via patients  
22                  and patient groups in the science decision-

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1 making process.

2 I would also say they also want to  
3 see less congressional involvement. And I  
4 think that is probably because of a negative  
5 feeling about Congress generally these days.

6 But I want to also just mention a  
7 few other things to keep in mind at the  
8 30,000-foot level, some things that haven't  
9 changed and some that have. I find them quite  
10 interesting.

11 One is that people continue to  
12 see, overwhelmingly see the value of science  
13 and scientists. And one new thing that we have  
14 been taking a look at, we found that people  
15 see the value of what we would call in this  
16 room regulatory science, and they want  
17 Congress to find ways for academia and  
18 industry and Federal agencies to work together  
19 to accomplish this.

20 Now, people are very mixed in  
21 their views about what's more important, speed  
22 of regulatory approval or safety. It's been at

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1 about 50/50 for a long, long time, and they  
2 are looking for experts to help them wend  
3 their way through deciding what's more  
4 important. Ultimately, they want both, and  
5 that's where we get back to the power of  
6 putting more evidence to work and regulatory  
7 science support.

8 There's strong support for  
9 cooperation and coordination among the various  
10 aspects of the science enterprise, academia,  
11 industry, and government. And this flies a  
12 little bit in the face of concerns about  
13 conflict of interest.

14 I personally think that those  
15 concerns boil down to people being unhappy  
16 about, angry about bad actors in the system,  
17 and of course they should be angry about it.  
18 But, ultimately, they want the various  
19 aspects, parts of the enterprise to work  
20 together.

21 People also say that not only do  
22 they support basic science strongly -- that

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1           hasn't changed for 25 years at least that data  
2           has been collected -- they're also strongly  
3           supportive of clinical trials, again, a little  
4           bit in the face of some of the things we see  
5           in the media and elsewhere and so-called  
6           conventional wisdom about resistance to  
7           clinical trials.

8                       In fact, what people say is the  
9           main reason that they haven't been engaged in  
10          clinical trials, clinical research generally,  
11          is that they haven't been asked. Only 6  
12          percent of the population say that their  
13          medical provider, their physicians ever talk  
14          to them about research of any kind.

15                      So, getting into the conversation,  
16          talking more, everybody involved in the  
17          science community needs to do a better job of  
18          talking about research. Sixty-three percent of  
19          the American public can't name a living  
20          scientist. A similar percentage can't name  
21          anyplace -- anyplace -- where science of any  
22          kind is conducted. Science is a little too, a

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1 lot too invisible in our society, given the  
2 way people value it. So, it's really time to  
3 put that human face and personal story of  
4 science out there, because the public will  
5 embrace it.

6 So, I would say to NIH and FDA and  
7 everybody in the science enterprise that, in  
8 order to speed the day that more resources and  
9 a better policy environment is available to  
10 us, we all need to be talking more about  
11 research and development and delivery of  
12 products, i.e., outcomes and solutions and  
13 answers and better health, than only talking  
14 about research.

15 There's a change in my own  
16 thinking. I think it's increasingly necessary,  
17 and I think we can do it.

18 MEMBER KATZ: Thank you, Mary.

19 Bill?

20 MEMBER BRODY: Okay. I was going to  
21 take my moderate hat off and say, look, this  
22 is a systems problem. We have the issue that

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1 Dr. Baum mentioned. It is not the cost of  
2 getting an approved drug through; it's the  
3 cost of all the failures that are both infant  
4 and adult mortality.

5 We have a problem with time to  
6 approval, and you have the FDA, which really  
7 views safety as 90 percent and is risk-averse  
8 because of the way they operate and report to  
9 Congress. I'm not being critical of the FDA. I  
10 think you get called on the carpet when things  
11 go wrong. You don't get praised as well when  
12 things go right. And it goes back to Kahneman,  
13 the economist, who said people were more  
14 worried about risk than they are about gain.

15 Then you have the issue where  
16 companies are going abroad to get their FDA  
17 approval. And then we have a conflict of  
18 interest.

19 But the topic today is really,  
20 what can the NIH do with the Cures  
21 Acceleration Network? So, we have to figure  
22 out, what are the levers that we can pull,

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1           that we might be able to pull, that could  
2           implement what is otherwise, I think, a big  
3           systems problem which is bigger than all of us  
4           to try to solve?

5                        So, I would like to kind of open  
6           it back up. I think the comments were all very  
7           helpful and insightful, and including Dr.  
8           Goodman and Dr. Baum, to weigh in: what  
9           should be the role of the NIH in this?

10                       And I don't know, Arthur, do you  
11           want to intercede now or do you want to wait?

12                       MEMBER RUBENSTEIN: I'll wait.

13                       MEMBER BRODY: Okay.

14                       MR. BERGER: Could I begin by  
15           asking a question? What is the interface right  
16           now with private enterprise, private  
17           companies, private pharmaceutical companies,  
18           and the NIH right now?

19                       I know there are many interfaces  
20           and scientific meetings and presentations, but  
21           harking back on what Ms. Woolley said there,  
22           there seems to be a large possibility for the

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1 NIH to sell itself better or interact more  
2 fully with the private industry stakeholders.

3 MEMBER KATZ: So, I think the  
4 answer to that question would be, could be  
5 answered by many of the institute Directors  
6 here, starting with what I mentioned with  
7 regard to partnerships in pre-competitive,  
8 building research/resources that many can use.

9 Other partnerships, maybe Tony and  
10 Susan can just provide examples of those.

11 MEMBER FAUCI: It really varies  
12 enormously, the spectrum, from very close  
13 collaboration at the clinical trial level with  
14 a product that a company is developing either  
15 for licensure or, less likely, companies tend  
16 to like to do it on their own, to how to use  
17 the combination of drugs like with HIV. That's  
18 one.

19 But the one that I find, I think,  
20 the most productive is something we're just  
21 beginning to accelerate more now. We have been  
22 doing it in drips and drabs. It's to try to

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1 get a concept from one of our basic  
2 researchers who might publish a paper that  
3 they would only think: I'm going to publish it  
4 in *Nature* or *Science* and then I'll go to my  
5 next paper. It's to try to get that on a track  
6 towards translation and development by  
7 providing for them research, resources, animal  
8 models, linking them to the regulatory  
9 process.

10 And this is one of the things that  
11 Jesse was alluding to in his comments, is  
12 something that we're now calling the Concept  
13 Acceleration Program, of trying to have the  
14 NIH as the basic science aspect of it, even  
15 though we do a lot of clinical translational  
16 research, to try to link them to companies to  
17 ultimately develop it.

18 So I think that the spectrum is  
19 large, but I'm particularly attracted by that  
20 aspect of what we have been doing for the last  
21 year or so.

22 MEMBER SHURIN: I think that one of

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1 the key issues is certainly the huge focus on  
2 the scientific issues and looking at  
3 mechanism. That's why the waste of information  
4 from not learning from the failures is so  
5 distressing to us.

6 At NHLBI, we have a lot of  
7 interactions with industry. Most drug  
8 development in recent years has been,  
9 particularly in cardiology, has been in  
10 industry and not by the NIH.

11 And our focus usually is on the  
12 kinds of things that industry won't be  
13 interested in. So those are often rare  
14 diseases or disorders in which there's not a  
15 huge profit margin for any of a number of  
16 reasons, including the fact that things may no  
17 longer be on patent.

18 And the issue that somebody  
19 mentioned about combination therapies where  
20 you have different companies is certainly one  
21 of the things that I think is of particular  
22 interest to us.

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1                   We also know that there is a  
2                   tremendous amount of stuff which is of both  
3                   scientific and clinical interest to us in  
4                   which there have been studies that have never  
5                   been published. And those create tremendous  
6                   difficulties for us, because often we're asked  
7                   to fund studies which we think have probably  
8                   already been done for which there's an answer,  
9                   but we don't know what they are.

10                  So I think that those are the  
11                  kinds of areas in which an intersection with  
12                  the NIH -- we would love to provide the  
13                  mechanism to both learn from the science and  
14                  learn about the diseases while studying drug  
15                  development.

16                  MEMBER KATZ: So I would like to go  
17                  back to the question that Bill asked in terms  
18                  of how you see the NIH facilitating this type  
19                  of interaction or being involved, to address  
20                  some of the challenges and to catalyze the  
21                  path to translation.

22                  DR. PERAKSLIS: I can try to take

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1           that. A few things that came to mind, you  
2           know, one, I talked about the open source  
3           thing again, right? It's very difficult for me  
4           to give data away when I want to. You know,  
5           taking support from a pharmaceutical company  
6           for certain investigators at certain  
7           universities is tough. Some companies have  
8           chosen to spin off a nonprofit, which you  
9           could do, and possibly NIH could be somewhat  
10          of a convener or an honest broker for some of  
11          that, to set up some of these consortiums.  
12          That might be a possibility.

13                 The other one, as I think about  
14          translation, and I really focus on it, really  
15          the translation part is really going across  
16          different scientific and medical domains,  
17          right, and making decisions in pre-clinical  
18          that now become hypotheses in clinical.

19                 You're           also           potentially  
20          propagating error as you go, you know, as you  
21          look at studies translational, so you're  
22          looking across those ways. So I think a lot of

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1 biotechs and biopharmas and even pharma, when  
2 we're very therapeutically-focused, may not be  
3 seeing some of those larger areas that could  
4 be propagated in. So I think there's something  
5 there.

6 And the concept of patient  
7 solutions versus products, I think a lot in  
8 industry think about products, not so much  
9 solutions. So oncology products that are mixed  
10 with skin care and are mixed with a  
11 nutraceutical, you know, is an interesting  
12 thing. Or not only common with therapeutics,  
13 but, again, the combination of diagnostics  
14 with something or a device and a delivery  
15 system.

16 So, if you point to science, the  
17 way to translate across looks like some  
18 opportunity that came to mind.

19 MEMBER KATZ: Yes, Ms. Selig?

20 MS. SELIG: Just one thing I might  
21 add, again, from my perspective, that might be  
22 a useful thing. I know you're going to have a

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1 session later on today, or maybe it's  
2 tomorrow, in terms of communicating with the  
3 public.

4 But speaking from someone inside  
5 of a nonprofit that's trying to do innovative  
6 things and isn't maybe as encumbered, in fact,  
7 isn't as encumbered at all as the NCI is or  
8 NIH or even these academic institutions that  
9 we fund, you know, I would encourage as much  
10 as possible better outreach.

11 Sometimes groups like ours get  
12 sort of pigeonholed into kind of the patient  
13 advocacy space, and there's sort of a certain  
14 kind of dialog that occurs, you know, a  
15 particular set of staff in a particular  
16 office.

17 I sit on the NCI DCLG, and I  
18 admire and I think that that's a very  
19 important function that happens. But in this  
20 space, maybe it's a little bit different.  
21 There are groups like ours -- there's a whole  
22 slew of us now out there, not just in cancer,

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1 but across diseases -- that are doing really  
2 innovative things in terms of finding and  
3 funding research and trying to develop  
4 collaborations and break down barriers.

5 So, I would welcome an enhanced  
6 way to understand all the different pockets of  
7 NIH that relate to what we're doing, and,  
8 also, to know that we are really making the  
9 best use of our limited dollars to leverage  
10 what you are already doing.

11 I don't have a specific example to  
12 bring to mind, but I feel in my short time  
13 doing what I have been doing, I find it very  
14 confusing, all of the different programs that  
15 exist, pockets of this kind of work that are  
16 going on.

17 I know it's difficult. It's a big  
18 enterprise. It's trying to do a lot of things.  
19 But perhaps we can be helpful if we could  
20 expand our dialog.

21 MEMBER KATZ: Thank you.

22 Arthur and then Harold.

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1                   MEMBER RUBENSTEIN: And I wanted to  
2                   ask this question, although it will sound  
3                   nihilistic, I think. I just wonder, having  
4                   thought about all this for a while, how  
5                   possible it is that all these things we're  
6                   talking about, all this money, all these  
7                   collaborations, all this issue about  
8                   intellectual property, actually won't make any  
9                   difference in the long-run. And what actually  
10                  the issue is, there are just cycles of science  
11                  that allow drug development to occur, and then  
12                  there are periods when it won't occur. And all  
13                  these things that we process don't actually  
14                  make much more than marginal difference.

15                 And I've been impressed by looking  
16                 at people looking at the economy, and they  
17                 have all these views of what affects it, but  
18                 then there are people who think it just goes  
19                 in cycles, and these other issues do moderate  
20                 it some, but they're not the critical issue in  
21                 terms of long-term view of it.

22                 And I just worry that we'll do all

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1           these kind of things, and on the margin they  
2           may be minimally helpful. Eventually, because  
3           of all the basic science and the genome  
4           information and so on, all this will come  
5           together, and we'll have another beautiful  
6           period of drug development, and we won't have  
7           any impact on what will come out.

8                       I hate to say it, but I would  
9           really like to hear what some of the  
10          scientists think about that kind of thing.  
11          Because we have had such an effort and so many  
12          brains and so many ideas about all this, and  
13          it seems to make rather little difference at  
14          this time. But that may just be a sign of age  
15          or something; I don't know.

16                      MEMBER KATZ: But don't you think  
17          we have to try?

18                      MEMBER RUBENSTEIN: I didn't say we  
19          shouldn't try. I'm just saying the try will  
20          have rather minimal effect, and eventually the  
21          science will come together to allow us to  
22          develop all these things as we always did. And

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1 we'll say it worked.

2 (Laughter.)

3 MEMBER KATZ: Harold?

4 MEMBER RUBENSTEIN: I would just be  
5 interested in people's ideas about that.

6 MEMBER VARMUS: My hand wasn't up,  
7 but I will respond. You just think I always  
8 want to say something?

9 (Laughter.)

10 But I will say something in  
11 response to Arthur, which is that, you know,  
12 regardless of whether you think this is a  
13 cyclic phenomena that is beyond our control or  
14 not, we do have something that is on the table  
15 here that I think NIH needs to hear about from  
16 these folks. That is the Cures Acceleration  
17 Network.

18 There is going to be money given  
19 to us, and it will be taken out of something  
20 else rather than added on. But, nevertheless,  
21 there will be an imperative to do something.  
22 Those of us around the table who run some of

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1 the larger institutes already have a fair  
2 amount of investment in translational and  
3 therapeutic development programs.

4 I'm trying to understand, and I'm  
5 not getting the message yet, what our invited  
6 experts think NIH should do with added money  
7 in this area because it's not a trivial  
8 exercise. It's likely to be \$50 million in the  
9 next year's appropriation. Viewed from the  
10 perspective of any large drug company, as you  
11 have seen, that doesn't mean anything unless  
12 you invest it very, very wisely.

13 So, I would like to know in a more  
14 pragmatic way, and I've been listening to  
15 discussions about how academic and government  
16 scientists get involved in drug development,  
17 make connections with companies, and so forth,  
18 but we suddenly have a very specific challenge  
19 given to us by the Congress, in a sense the  
20 public. I would like to know what you think we  
21 should do in response to that.

22 MEMBER CASSELL: Harold, I'm not

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1           sure they know about CAN and how much they  
2           know, maybe to answer that question. They do?

3                   MEMBER VARMUS: I don't know.

4                   MEMBER KATZ: Tony? And then we're  
5           going back to the panel.

6                   MEMBER FAUCI: So I will continue  
7           to direct the question and amplify a little  
8           bit what Harold just said.

9                   So, I'm hearing a bunch of things  
10          that I've heard a thousand times, if I might  
11          just say so. And that is there are multiple  
12          issues here, two major ones.

13                  The problem globally, industry,  
14          academia, what have you, of getting products  
15          translated, of success in developing  
16          interventions, be they diagnostics,  
17          therapeutics, or vaccines -- that's there.  
18          That's a given.

19                  Then there's the specific issue  
20          that we need help on. How does the NIH get  
21          involved in or improve its contribution to the  
22          translation towards these interventions?

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1                   And there's two subsets of that.  
2           There's the question that we not infrequently  
3           get asked: tell me what drug or what vaccine,  
4           or whatever, the NIH developed. Well,  
5           fundamentally, it's not our job to do that.  
6           It's our job to create the science to allow  
7           industry to do that.

8                   So, sure, there will be an AZT  
9           that will come along that we'll develop or  
10          there will be a dengue vaccine that we  
11          develop. But, for the most part, the  
12          interventions are going to be developed by  
13          industry.

14                   So, it would seem to me that in  
15          the issue of how we're going to use the CAN  
16          money that Harold was talking about, it is,  
17          how can we, NIH, use what we do to actually  
18          get involved in that translational process  
19          that ultimately has to involve industry?

20                   It's fantasy to think that we're  
21          going to take \$50 million, or whatever million  
22          dollars, worth of CAN money and in the

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1 Clinical Center or someplace else we're going  
2 to develop drugs. I don't see that.

3 So, I would like to hear from you  
4 how you think we can work together to get the  
5 process of cures done as opposed to we develop  
6 a cure; you develop a cure.

7 MEMBER KATZ: Hold that thought.

8 Francis?

9 DIRECTOR COLLINS: I just want to  
10 make one friendly amendment to Harold's  
11 question to expand it a little bit beyond CAN.  
12 While CAN is the new kid on the block here,  
13 this \$50 million that will probably flow next  
14 fiscal year, NIH has been developing and has  
15 actually some fairly powerful additional  
16 resources that fit into this conversation,  
17 including high throughput screening through  
18 the four centers that do that, that have the  
19 capacity of mid-sized pharmaceutical companies  
20 as far as throughput, and the ability,  
21 therefore, to train academic investigators in  
22 how to do assay development and application.

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1                   Add to that the Therapeutics for  
2                   Rare and Neglected Diseases Program, TRND. Add  
3                   to that, also, things like the GMP facility at  
4                   the Clinical Center that we talked about  
5                   earlier this morning, and the Clinical  
6                   Center's capability to do Phase I and II  
7                   trials, and the CTSAs which have that capacity  
8                   now, some soon-to-be 60 of those across the  
9                   country.

10                   So, don't limit your answer to the  
11                   question about what NIH should do just to the  
12                   CAN part, which is sort of focused on the pre-  
13                   clinical part. But what about this whole  
14                   pipeline of opportunities? What should we do,  
15                   what could we do, what might we do to be  
16                   synergistic with what already exists in the  
17                   private sector, but to speed up the potential  
18                   here, especially with all of the new drug  
19                   targets that are emerging for both rare and  
20                   common diseases that are not all being  
21                   followed up on right now?

22                   So, that's the broader question,

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1 but I sure would love to hear specificity in  
2 responses, if you can.

3 MEMBER KATZ: So, Garret, as a  
4 professor of translational medicine and  
5 therapeutics, do you want to start us off?

6 (Laughter.)

7 DR. FITZGERALD: So I hesitate to  
8 scoop myself as I'm stuck with giving a talk  
9 after lunch. But briefly, I will say that  
10 there are very concrete things that the NIH  
11 can do.

12 I really believe that there is a  
13 huge problem in terms of human capital. The  
14 number of people who practice, who pursue  
15 science nowadays in a way that straddles the  
16 translational divide, and in their own  
17 experience integrates the rigor of basic  
18 science with the practical realization of  
19 clinical research, has diminished alarmingly.  
20 And the number of those that know anything  
21 about drugs is almost down to counting on two  
22 hands.

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1                   And I think we're paying a huge  
2 price for that. Those people play a catalytic  
3 role at the point of greatest failure in drug  
4 development, which is proof-of-concept in  
5 Phase II. They are the people who understand  
6 mechanism and extrapolate the information from  
7 model systems into sophisticated science in  
8 humans.

9                   And I think that is very pertinent  
10 to our failure to realize the potential of the  
11 great strides in basic science and translation  
12 to therapeutics. I think it's very relevant to  
13 our limitations in terms of risk detection in  
14 regulatory agencies. I think it's very  
15 relevant to the fact that our physicians get  
16 their information about new drugs from exactly  
17 the same place as our patients do, and that is  
18 from direct consumer advertising.

19                  And I think it's extremely  
20 relevant to comparison effectiveness, where  
21 expertise in this domain plays no role in this  
22 country, but does in the UK, for example.

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1                   So I think human capital is the  
2 top of the list. It's a role that the NIH can  
3 play a central role in.

4                   I think in terms of programmatic  
5 investment, I think a really important thing  
6 is actually aggregating the existing resources  
7 and expanding them, but in a way that is,  
8 then, bundled and visible to the relevant  
9 community, and intertwining that with  
10 initiatives to develop critical mass in TMAT,  
11 because these people have to have a career  
12 path.

13                  And more importantly, they have to  
14 be engaged by thinking this is the really hot  
15 area of science, and that's why I'm going to  
16 sign up and train in it. And presently, that's  
17 absolutely not true.

18                  So we have a very segmented  
19 scenario at the moment, and it is people that  
20 make things happen rather than structures. So  
21 I would really put the emphasis on people.

22                  MEMBER VARMUS: Can we follow up on

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1           that a little bit? I may?

2                   Are there some very specific  
3 programs that you would view as models for the  
4 kinds of training enterprises that work well?

5                   DR. FITZGERALD: Well, I mean,  
6 again, I'll talk about this when I talk.

7                   MEMBER VARMUS: Okay. Fine.

8                   DR. FITZGERALD: But I mean, just  
9 to answer specifically, for example, and as  
10 I'm sure you're aware, the Wellcome Trust  
11 launched a program about three years ago now  
12 where they funded four centers in  
13 translational medicine and therapeutics, where  
14 the academic bidders were encouraged to have  
15 close interaction with industry in their  
16 bids -- that was actually a requirement -- and  
17 where the focus was on creating this type of  
18 interdisciplinary skill set in a new  
19 workforce.

20                   DR. DUNCAN: So maybe I can address  
21 some of the neglected disease issues. I mean,  
22 I mentioned earlier, you know, we just really

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1 need more effort in this space, but that is  
2 not the answer you are looking for.

3 It's not simply just building more  
4 capacity and more projects. It's more about  
5 thinking smartly about how you pull these  
6 projects together. So, how we bring together  
7 the best of the private industry, who is not  
8 really going to invest that much in this  
9 space, with the best academic researchers.

10 And some of that is actually about  
11 doing things which are already being done and  
12 taking concepts and pulling them into  
13 potential products.

14 What has tended to happen is that  
15 you have this huge expansion of genomic  
16 information, and there's hundreds of targets  
17 here. The thing that was recognized fairly  
18 early on in the commercial markets, and this  
19 applies exactly the same in the neglected  
20 disease space, is that it's all about just a  
21 small number of well-validated targets.

22 And yet, trying to get the tools

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1 and the information together to get those  
2 well-validated targets is very, very hard. It  
3 tends to be done today by individual academic  
4 investigators who are doing one target after  
5 another, and that's what they make their  
6 career. Even if it's not well-validated,  
7 they'll still continue to pursue it.

8           Whereas, what we really need is a  
9 more integrated, more comprehensive type of  
10 effort in some of the neglected disease space  
11 that we just do once and for all. Build the  
12 right set of tools, get the small number of  
13 validated targets, and then do a huge effort  
14 behind doors, where you know you're likely to  
15 be much more successful.

16           So, I think a more focused effort  
17 would help. And I think that building the  
18 teams issue for me is around saying, can you  
19 get the right expertise to work with the  
20 investigators who've got the right tools?  
21 Because, again, at the moment, it's often  
22 they're around saying we need one piece of

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1 information. So there may well be an NIH  
2 contract. You can look to that contract, and  
3 you can be lined up, and eventually get that  
4 piece of information.

5 Sometimes it takes a long time.  
6 The feedback I hear is that it takes a long  
7 time, and it's not necessarily with a lot of  
8 intellectual input, which is often concerning  
9 as well.

10 So, in other words, without  
11 designing the right study, sometimes you get  
12 half the story because you may, for example,  
13 look for some pharmacokinetics around  
14 something, but, basically, what you can get is  
15 one type of data and not necessarily address  
16 the specific question that would help move a  
17 project forward.

18 So, that comes back to the issue  
19 of, I think, having fewer types of projects  
20 and more focus on things which are actually  
21 needed in the clinic and not necessarily some  
22 of the projects which are interesting, but

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1 would never necessarily be taken up by  
2 industry or taken up by any of our current  
3 development partnerships, because they address  
4 a therapeutic need that's, quite frankly,  
5 interesting, but it is not really what is the  
6 critical need in that particular area.

7 DIRECTOR COLLINS: Can I just come  
8 in briefly and just ask a question? Because  
9 one of the features of the Cures Acceleration  
10 Network is to give NIH, at least a part of the  
11 funds, the ability to function in the way that  
12 DARPA does, where you bring in a project  
13 manager that is authorized to acquire  
14 resources when needed and a quick turnaround  
15 time, and also to kill projects quickly that  
16 seem not to be meeting their milestones.

17 Are you referring to that kind of  
18 model as something that's currently missing?  
19 Would you want to comment on that?

20 DR. DUNCAN: That is the sort of  
21 thing that I think is needed. Certainly from  
22 my perspective, to a certain extent, we at the

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1           Gates Foundation are able to work that sort of  
2           way where we can move resources around a bit  
3           more easily. But I think there is that making  
4           quick decisions and moving the funds to where  
5           they're needed.

6                       MEMBER KATZ: Go ahead, Gail, and  
7           then Jesse.

8                       MEMBER CASSELL: I am a little bit  
9           out of my league here, but what I would  
10          suggest, Francis, is that one area that I see  
11          as a potential opportunity for NIH is perhaps  
12          a greater investment in the whole area of  
13          chemical diversity and bringing back the  
14          natural product that so many of the companies  
15          got away from.

16                      Other countries, China, South  
17          Africa, and others, are investing heavily in  
18          building natural product libraries. But yet,  
19          we don't have good chemists, many of them,  
20          experienced in natural products.

21                      New technology in the area of  
22          synthetic biology, like the Vintra Institute

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1 is exploring, I think, and the possibility of  
2 being able to increase chemical diversity  
3 using that technology would go a long way.

4 And the other area, I think, that  
5 I see is more research in issues around  
6 bioavailability. If you look at the biggest  
7 losses, particularly in development of anti-  
8 infectives, but also oncology, and all  
9 therapeutic areas, this issue of non-oral  
10 bioavailability, new mechanisms for drug  
11 delivery, aerosol biology in particular -- I  
12 realize that some of this is controversial,  
13 but I think we still have yet to fully  
14 explore. You know, aerosol delivery is a great  
15 alternative to issues that challenge oral  
16 bioavailability as well.

17 MEMBER KATZ: Thank you.

18 Jesse?

19 DR. GOODMAN: The major comment I  
20 wanted to make is I think, as you do this, you  
21 should build on what is NIH and the academic  
22 community that it is most connected to. You

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1 know, what are the strengths and how do you  
2 link those to the other parts of the system?

3 And this is kind of going to  
4 Garret's comment. I think you could spend --  
5 but a little beyond it -- I think you could  
6 spend a lot of energy trying to change a horse  
7 into a giraffe, and in reality this isn't that  
8 much money. And the thing to think about would  
9 be, how can you catalyze in areas where  
10 there's promising discovery, bringing yourself  
11 together with the right people to then get the  
12 job done?

13 So some of that is a DARPA model,  
14 but a lot of it is about partnering with the  
15 right people and getting them to do their  
16 parts of this module and do it in a managed  
17 way.

18 I think a longer-term project, his  
19 comment about training is important. However,  
20 unless we create a reward system in science  
21 and academia that actually rewards the health  
22 outcome rather than the individual

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1 accomplishment and the paper in *Science*, that  
2 ain't going to happen.

3 So, I mean, in the long-run, I  
4 don't have the answer, but I think we need to  
5 think about a model that rewards patient and  
6 scientific outcomes other than just  
7 publications.

8 I can't let Dr. Brody's comment  
9 go. Well, you said it.

10 You know, I need to correct a  
11 misconception around this. You know, if there  
12 are products that work and help people, they  
13 will get out of the FDA very fast. There is  
14 not a bunch of stuff sitting around that  
15 provides radically new or even substantial  
16 incremental therapies that our staff would not  
17 celebrate getting out as quickly as possible.

18 I think the problem is, when you  
19 have marginal benefits or diseases that aren't  
20 that serious, and then people look at risk and  
21 benefit in that context, you know the public  
22 is our customer and they are concerned about

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1 the safety of products.

2 I think, as you saw with the  
3 rotavirus decision and how that was handled,  
4 when we see a product with clear benefit,  
5 we're able to look at it and try to weigh risk  
6 in a science-based way. That is part of  
7 building our scientific capacity, is to assure  
8 we make the best risk-based decisions.

9 But this sort of seconds Arthur's  
10 comment a little. I think there is something  
11 going on out there right now in the science  
12 cycle where there's a lot of incredibly  
13 promising science and information that hasn't  
14 yet moved forward.

15 But I think that's a good reason  
16 to do these activities, because maybe we're  
17 catalyzing -- you know, it's like catalyze the  
18 degradation of the oil in the ocean. Maybe we  
19 can catalyze the transition of some of these  
20 discoveries into science, into products. I  
21 think that's the interface where NIH should  
22 work.

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1 MEMBER KATZ: Thank you.

2 You heard that we're not going to  
3 go into the billion dollar business of drug  
4 development, but this Cures Acceleration  
5 Network may be authorized, may be appropriated  
6 for \$50 million next year, but it's authorized  
7 for up to \$500 million.

8 And you've heard what Francis  
9 talked about in terms of some of the resources  
10 that we have at least to take something that  
11 would be more realistic as a potential  
12 product.

13 But I would like for you to  
14 respond to where we are with that, more than  
15 potential.

16 DR. BAUM: Yes. I think it's one of  
17 the areas that seems to me makes a lot of  
18 sense, is in the area of rare diseases. And  
19 where you have a clear genetic defect, maybe  
20 even if you don't, that you can do the science  
21 to evaluate that patient population, that  
22 you're sort of uniquely positioned to do that,

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1 to get access to those small sets of patients  
2 which no one has enough of to really know  
3 exactly what to do, and to do clinical trials  
4 in a reasonable timeframe.

5 So, I think that's something that  
6 could be actually a near-term opportunity to  
7 show real benefit and real advance  
8 therapeutically in a short period of time.

9 And our company -- there's others  
10 that are interested in rare diseases. So  
11 forming some sort of consortium around that, I  
12 think, would be really a great idea and would  
13 facilitate it happening much sooner.

14 So, I think that's the kind of  
15 thing I see as being a unique thing that could  
16 be done in the near-term, but I think there's  
17 many others as well. And one of the key ones,  
18 I think, is around biomarkers and patient  
19 selection because, as you have seen many  
20 times, it is not always obvious what  
21 biomarkers we should be looking at. And if  
22 they are not validated ahead of time and you

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1 don't have a diagnostic, you can't really use  
2 them in clinical trials. You have to learn  
3 through doing those trials what you can apply  
4 next time. So you almost validate the test and  
5 the drug at the same time in some of these  
6 cases.

7 So, is it possible, using standard  
8 of care and looking at patient populations,  
9 you could help define biomarkers that will be  
10 useful to therapeutic development for those  
11 people who are pursuing those particular  
12 approaches?

13 So, I think that background  
14 information is just missing in many cases. So  
15 I know in inflammation and immunology we  
16 struggle to know what to do in lupus. What are  
17 we affecting? How can we realistically follow  
18 it and know that we can make some kind of  
19 effect on a small patient population before we  
20 have to do Phase III trials? Those kinds of  
21 things, I think, are really also near-term  
22 benefits that could come out of the

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1 collaboration with the NIH.

2 MEMBER KATZ: I would just  
3 reinforce one thing that Francis said. That is  
4 that, going back full circle to this morning's  
5 earlier discussion, the Clinical Center, one  
6 of the great resources is the collections of  
7 rare patients in many areas.

8 DR. BAUM: I think that is an  
9 incredibly unique asset, and one that you can  
10 take advantage of.

11 MEMBER KATZ: Francis?

12 DIRECTOR COLLINS: So, I think rare  
13 disease applications are, in fact, compelling,  
14 and there is the Therapeutics for Rare and  
15 Neglected Diseases Program which is already  
16 funded, which is just beginning to get  
17 started, and maybe we'll hear a little bit  
18 more about it this afternoon.

19 But I want to push you about the  
20 common diseases, because certainly in that  
21 category we have a lot of new targets, things  
22 that are potentially drug-able, but who knows?

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1 If you look at the outputs from genome-wide  
2 association studies, which haven't told us  
3 very much in terms of big risk factors that  
4 are highly valuable for making predictions  
5 about future illness, but they are, after all,  
6 pointing towards pathways that must be  
7 involved in pathogenesis.

8 And I think most people would  
9 agree that there's probably really no linear  
10 relationship between the odds ratio of a  
11 particular variant in a particular gene and  
12 whether that actually is an interesting drug  
13 target.

14 After all, when you look at the  
15 cholesterol scan by genome-wide association  
16 studies, well, you find all of the known drug  
17 targets, including HMG-CoA reductase, although  
18 the odds ratio is key. It just means that the  
19 spectrum of variation that nature has  
20 tolerated or evolution has tolerated in human  
21 populations is pretty limited for really  
22 important protein products.

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1                   So, there are hundreds of these  
2                   now, and I guess my sense is not only do we  
3                   have rare and neglected diseases, but we have  
4                   rare and neglected targets for common  
5                   diseases.

6                   So, I would be interested in your  
7                   perspective from Pfizer's focus now on human  
8                   genetics. Are those targets being adequately  
9                   mined, or is there a need there for greater  
10                  activity?

11                  DR. BAUM: So, yes, I would say  
12                  there is, and I was thinking of it more as  
13                  different timeframes, and that in the near-  
14                  term those rare diseases is something to show  
15                  something clear quickly. But I think the real  
16                  benefit is down the line.

17                  How can we subset possibly those  
18                  patient populations with hypercholesterolemia  
19                  into those that should be treated with  
20                  particular regimens? That would be incredibly  
21                  valuable. In diabetes, I think we have similar  
22                  problems. Who should we be treating and how

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1 with these new agents? And how we might be  
2 able to use combinations in particular  
3 patients that have complementary pathways that  
4 are affected.

5 So, I think there's lots of that  
6 sort of work that would be a huge benefit to  
7 the community in general in sort of a pre-  
8 competitive kind of research that could be  
9 done.

10 So, I agree, and I think that some  
11 of the problems with not being able to show  
12 advances in many of these more common diseases  
13 is because we're looking at actually five  
14 different subsets of patients all at the same  
15 time. So the benefits are incremental.

16 But if we could focus on those  
17 patients that show the greatest benefit, then  
18 maybe we would have something that's more  
19 clear to the FDA. That is a benefit, making  
20 the whole process run more efficiently and  
21 more quickly for all of us. So, I think those  
22 are places that there could be benefit.

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1                   In terms of that same question, I  
2                   think the combinations I brought up briefly,  
3                   but the combination I think is really a key  
4                   benefit, too, because you can bring together  
5                   different companies or academic institutions  
6                   to have a combination therapy that looks like  
7                   it's really going to leapfrog over the current  
8                   incremental single-agent approaches. So, to  
9                   me, that's another place that the NIH could  
10                  uniquely get involved and help facilitate that  
11                  kind of interaction and collaboration.

12                 DIRECTOR COLLINS: If I push a  
13                 little, because it sounds like you are  
14                 primarily talking about taking existing  
15                 targetable pathways and figuring out smarter  
16                 ways to utilize the agents that come out of  
17                 that.

18                         What            about           entirely           new  
19                 molecular --

20                         DR. BAUM: Oh, yes, absolutely.

21                         DIRECTOR COLLINS: -- focused on  
22                 targets that we haven't previously known

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1 about?

2 DR. BAUM: Yes, absolutely. Because  
3 I think the identification of targets and the  
4 biology behind those targets is probably  
5 better done by the NIH and academics than we  
6 have done. So I think there's a huge  
7 opportunity there.

8 And maybe some of the efforts you  
9 were talking about earlier of making that  
10 connection, so that the researchers know how  
11 to make that next step, that they actually  
12 would, and that we would see an acceleration  
13 of the wave of innovation. Maybe it will  
14 happen anyway, but if we could accelerate it,  
15 I think that would be a great accomplishment.

16 MEMBER VARMUS: Could I build on  
17 that just a little bit? I'm glad that Francis  
18 brought back the target issue, because it does  
19 seem to me that NIH should not be confining  
20 itself to rare diseases, and especially in the  
21 area of cancer, where the number of targets  
22 that we're identifying through the genomes is

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1 enormous.

2 It seems to me there is a place  
3 where some kind of consortia relationship with  
4 industry might work, and we've had such  
5 relations before in areas, for example, CDA  
6 sequence. These are not things that are likely  
7 to be detected by IP arrangements, and  
8 validating targets is not an easy process.  
9 There are an awful lot of things on the table  
10 at the moment.

11 If there were some way for a major  
12 industrial firm to collaborate either  
13 intramurally or extramurally in a way that  
14 would get those targets out there on the table  
15 for the public benefit, it seems to me that  
16 this is something that we ought to be  
17 exploring a little more assiduously.

18 DR. BAUM: Yes, I agree completely.  
19 And one of the things that I was going to ask  
20 you, actually, was if you could meet with Jeff  
21 Kindler and the head of R&D to talk about  
22 something like that, because I think that's

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1           really --

2                       MEMBER VARMUS: I've only been  
3           approached by email. I'm not sure this is  
4           right for public discussion.

5                       (Laughter.)

6                       DR. BAUM: But I think that it's  
7           definitely something of interest, and it's the  
8           idea of this consortium. We need more  
9           interaction on that front.

10                      MEMBER TABAK: So, just to remind  
11           everybody, there is one other asset that  
12           hasn't really been mentioned, and that's the  
13           Biomarkers Consortium, which the Foundation  
14           for NIH has convened.

15                      At the table are NIH, FDA, and  
16           industry, including many of the companies that  
17           we have heard from today. The whole gist of it  
18           is to do things in the so-called pre-  
19           competitive space. There have been some  
20           successes. Just sitting at the table is a  
21           success.

22                      But many of you have alluded to

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1 the need for biomarkers. I'm just curious as  
2 to what more you think we need to do. Or is it  
3 just we need to do more?

4 MEMBER VARMUS: We need to do  
5 something that works well.

6 (Laughter.)

7 DR. BAUM: A lot of things we have  
8 done have been talking, but not the true sense  
9 of collaboration and where we both have skin  
10 in the game, where we really have something  
11 that we both have strong interest in. So,  
12 you're going to make sure it comes to  
13 fruition. I think that's been a problem,  
14 traditionally, that it just hasn't come to the  
15 next stage because people have discussed it,  
16 but not invested in it.

17 MEMBER BRODY: Dr. Rubenstein? And  
18 then I think we'll open it up to the general  
19 public.

20 MEMBER RUBENSTEIN: To move from  
21 being nihilistic, my colleagues in the  
22 Alzheimer's field, under the aegis of the NIMH

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1 and our relations with industry, have, I  
2 think, moved pretty quickly in the last couple  
3 of years to develop, first, a very interactive  
4 consortium that is very broad and come up with  
5 a number of biomarkers that weren't there in  
6 the past that they feel very optimistic about.

7 Leaving aside exactly what one's  
8 view of that is, I actually have been  
9 impressed by both the collaboration of these  
10 individuals, the extent of the consortium,  
11 which is right across the country, and maybe  
12 it's international, and also the relationship  
13 of not-for-profit organizations, the  
14 Alzheimer's Foundation, and so on.

15 When I have looked at that and  
16 been to some of their meetings, I must say  
17 that many of the things we have talked about  
18 here, they seem to be well underway and very  
19 enthusiastic and collaborative about. It just  
20 may be worth -- that is already in the NIH, of  
21 course -- it just may be worth looking at some  
22 of the things that have already pushed forward

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1 rapidly recently and taking some best-case  
2 scenarios from them. It's just an example that  
3 I have found very positive actually.

4 MEMBER KATZ: Dr. Hodes maybe would  
5 like to inform that as well.

6 MEMBER HODES: No. I am happy to  
7 comment again. That will be a topic of  
8 tomorrow morning's session when we're talking  
9 about public/private partnerships. And among  
10 the examples are some of those which have been  
11 successful in this. If you prefer some comment  
12 now, I would be happy to do it. Otherwise, we  
13 will get into it in some depth tomorrow.

14 MEMBER KATZ: Please identify  
15 yourself.

16 DR. ROWE: Sure. I'm Steven Rowe  
17 from the University of Alabama, Birmingham.  
18 I'm a CFTR, a biologist, and cystic fibrosis  
19 scientist.

20 I was just going to hearken back  
21 to this need for subphenotyping that Dr. Baum  
22 spoke of. One of the areas that I've been

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1 thinking about more regularly is that of COPD  
2 or chronic obstructive pulmonary disease, and  
3 how one of the failures of those megatrials is  
4 that patients with severe bronchitis are  
5 lumped together with patients with no cough,  
6 and have severe emphysema. An improved  
7 molecular understanding of that disease could  
8 lend itself well to collaborations, both with  
9 small companies and large pharma. That could  
10 accelerate things.

11 The second point I would like to  
12 make is regarding the biomarkers and hearken  
13 back to the biomarkers. Perhaps NIH resources  
14 could be directed towards really improving our  
15 pre-clinical models, as we've looked, and  
16 those that are predictive of translational  
17 results.

18 For example, in CF science right  
19 now, there's been a new small molecule that  
20 activates CFTR. But, importantly, the pre-  
21 clinical model has been very predictive of the  
22 in vivo situation, which has facilitated much

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1 more interest from pharma in therapies of that  
2 type. So, perhaps it's an area of resources  
3 that could be directed.

4 MEMBER KATZ: Thank you.

5 DR. BERGAN: Yes, I'm Ray Bergan.  
6 I'm one of the panelists this afternoon. I'm  
7 Director of Experimental Therapeutics for the  
8 Lurie Cancer Center at Northwestern  
9 University. I'm a medical oncologist, and I  
10 run a basic research lab.

11 I think it's very important to  
12 highlight the point that we don't know what to  
13 do. We don't have a clear path forward. There  
14 is universal recognition that the process of  
15 drug discovery and development is inefficient  
16 and it's highly complex, but that's  
17 universally-accepted.

18 I think the key issue that we need  
19 to acknowledge before we can go forward is  
20 that we don't know what to do. And that, in  
21 fact, leaves a clear role for NIH. What  
22 government does very well, and NIH does in

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1 particular, is it recognizes large problems  
2 like this and devotes resources to them. It  
3 basically sets up incubator projects. And this  
4 is a perfect scenario to set up such incubator  
5 projects.

6 So, Dr. Collins, what you have  
7 done, and done very well, is through NIH, you  
8 put in the components of the existing drug  
9 discovery and development network. But, as we  
10 recognize, those components are not acceptable  
11 to us as they exist in their current form. So,  
12 basic questions are not answered.

13 Can the process be improved? And  
14 we don't know the answer to that. Everyone in  
15 this room, myself included, believes that they  
16 can. The facts, in fact, speak otherwise. It  
17 affects potentially new chemical entities, and  
18 times to bringing a drug from the bench to  
19 clinic haven't changed in a couple of decades,  
20 despite exponentially increasing cost.

21 So, I think it is a perfect  
22 opportunity to use the resources that could be

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1 coming to CAN and the resources that NIH has  
2 to basically put out large programs, U01s,  
3 U54s, and hand it out to investigators. Put it  
4 in little incubators, and let them come up  
5 with ideas.

6 Put in specific parameters. These  
7 are the problems. Make it hypothesis-driven.  
8 Answer a question. Require that they interact  
9 with companies. And, as always is the case,  
10 you will be imminently surprised and amazed at  
11 some of the creative ideas that come back.

12 MEMBER KATZ: So, I would just say  
13 that what Francis has put in place has not  
14 really been tested yet. So we are not yet  
15 ready to talk about failure.

16 Yes, Rob?

17 DR. CALIFF: Good morning. I'm Rob  
18 Califf from Duke, and I'll be on the panel  
19 this afternoon, too. So I'll be brief.

20 First, I just want to reemphasize  
21 what Garret said. And I'm sure, knowing him,  
22 he will emphasize it amply in his comments

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1           this afternoon.

2                       I think we really do, at the basic  
3           level of person power, a lot of people are  
4           being trained to do things, but not that many  
5           are being trained to work in this future world  
6           that we are sort of describing. It is very  
7           noticeable at the level of an individual  
8           active medical center, as I travel around and  
9           talk to people.

10                    I also agree with this concept  
11           that we sort of need -- it is sort of like a  
12           12-step program -- we need to admit that we  
13           are fairly ignorant and we are all struggling.

14                   Pfizer used to come to us and say,  
15           you know, "We want to buy into your discovery  
16           science, but don't tell us how to develop  
17           drugs, because we do it for a living and we're  
18           really good at it." Now they're coming saying,  
19           "We've got too many molecules, too many  
20           pathways. We don't know how to develop drugs.  
21           Can you help us do that?"

22                   (Laughter.)

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1                   Our answer is we don't know,  
2                   either, but let's try together.

3                   But the point I wanted to make  
4                   that might be a little different, I'm sure  
5                   everyone realizes, but I really want to  
6                   emphasize it: the really critically shortage,  
7                   to me, is informatics and quantitative  
8                   sciences.

9                   My response to Arthur's cynicism,  
10                  which I understand, is I think the new wave is  
11                  really integrating this amazing amount of  
12                  knowledge that we are overwhelmed with now  
13                  that is coming from things we could measure  
14                  that we just couldn't measure until very  
15                  recently. And we are all overwhelmed with  
16                  information coming at us, and we don't know  
17                  what it means. We are lacking enough talented  
18                  people who can help us arrange and structure  
19                  that information to turn it into knowledge.

20                  So, I still don't see adequate  
21                  funding coming in for training programs in the  
22                  very fundamental quantitative and informatics

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1 sciences. I think that's our most critical  
2 shortage that ought to be emphasized.

3 MEMBER KATZ: Thanks, Rob.

4 MR. SIMON: I am Greg Simon from  
5 Pfizer. I'm on a panel tomorrow morning.

6 I wanted to talk about the two  
7 comments Dr. Rubenstein made about, "Does  
8 anything we do matter?" and what Dr. Fauci  
9 said, which was that "I've heard it all  
10 before." And what are we going to do with the  
11 \$50 million or any other million that would  
12 make a difference?

13 I do think we have different eras  
14 in science. I think we have been leaving the  
15 small molecule blockbuster. And a lot of the  
16 failures that come out of the pipeline now  
17 were the last gasp of that kind of thinking,  
18 which is why so many failed studies now are  
19 being walked over to the people who can look  
20 at the responders retroactively,  
21 retrospectively, and say, what did we miss  
22 when we designed this trial many, many years

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1           ago, because we weren't doing that when the  
2           trials were designed. We're doing them now  
3           when they come out and they fail.

4                   The problem is in the era we are  
5           in now in terms of being able to target drugs  
6           based on genomic characteristics. We are still  
7           operating in a regulatory system that was  
8           built in the fifties, a disease categorization  
9           system that was designed in the 18th and 19th  
10          centuries, and a communications model to the  
11          public that came from the pre-internet era.

12                   So, if we don't change those three  
13          things, the progress people make on the  
14          genomic personalized medicine side is always  
15          going to be swimming upriver. As an example,  
16          you heard this morning how crizotinib helps  
17          certain kinds of basically non-smoking lung  
18          cancer patients who have a particular  
19          sequence. That should be an orphan disease,  
20          but the government says, no, we're not going  
21          to treat it as an orphan disease.

22                   We know that lung cancer is not

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1 one thing. If Pfizer developed a drug that  
2 cured 80 percent of lung cancers, but did  
3 nothing for the other 20, wouldn't they feel  
4 orphaned in the world of lung cancer?

5 And yet, we know the future is not  
6 going to be curing lung cancer. It's going to  
7 be curing people with this kind of a cancer  
8 and that kind of a cancer.

9 And all of the incentives we have  
10 to get people to focus on orphan diseases and  
11 rare diseases are not being applied because of  
12 disease categorizations that we inherited from  
13 the Germans and the French a long time ago.

14 What do you do with \$50 million?  
15 What is NIH's role? NIH often has a lot of  
16 these excellent consortia for one particular  
17 thing. The challenge is, how does NIH become a  
18 host of a virtual enterprise where they use  
19 that kind of money to administer programs that  
20 have begun with the end in mind? A lot of  
21 these consortia do not begin with the end in  
22 mind. They begin with a particular product in

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1 mind or a goal to identify something in mind,  
2 but that is not the end. The end is the  
3 therapy to a patient.

4 So, with all of the great  
5 resources of the Intramural Program and the  
6 talent in the Extramural and Intramural  
7 Programs, if NIH were to host the virtual  
8 enterprise made up of the resources that are  
9 here on the campus and begin with the end in  
10 mind of asking the question, given these  
11 resources and given the training we have,  
12 which industry groups, which nonprofits, which  
13 other countries' resources do we need to  
14 invite in for certain kinds of therapy  
15 products to be developed? And our role is to  
16 make certain that all of those pieces come  
17 together; the right piece at the right time  
18 from the right place.

19 Now, that implicates a lot of  
20 things. It implicates funding models. It  
21 implicates institutes sharing. It implicates  
22 conflict-of-interest regulations.

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1                   But what are all these resources  
2                   for, if not to create the base of an  
3                   enterprise that, joined with the private  
4                   sector, can accelerate therapy production  
5                   without NIH having to fund it all? But without  
6                   the seed and the coordination, if you will,  
7                   from NIH, there's really nobody hosting that  
8                   kind of virtual enterprise that links our  
9                   government, our universities, and our industry  
10                  together.

11                 So that's what I would suggest it  
12                 is. We are in an area where a lot of the  
13                 things we do won't make a difference if we  
14                 don't change our assumptions. And NIH has a  
15                 huge future role to play as the host of this  
16                 virtual enterprise, but it has to figure out,  
17                 does it want to do that, and then is it  
18                 willing to organize around that concept?

19                 MEMBER BRODY: Well, we've heard --

20                 MEMBER VARMUS: I would just make  
21                 one brief comment. I agree with virtually  
22                 everything that Greg just said. It was a very

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1           useful, thoughtful statement.

2                       But I'm a little concerned that in  
3           my earlier comment I overly focused on the \$50  
4           million in CAN money. For reasons that  
5           actually have been articulated by some of my  
6           colleagues, (a) that money, that amount is  
7           likely to grow; (b) it actually is only a  
8           small amount of what NIH, especially some of  
9           the larger institutes, are already spending in  
10          this domain of target identification, drug  
11          development, basic science that feeds drug  
12          development, drug testing, clinical trials,  
13          networks on a very large scale.

14                     And I agree. I brought it up. I  
15          and many of my fellow institute directors are  
16          a little concerned about how the CAN  
17          initiative gets coordinated with other things  
18          that we're doing, which is a way of saying  
19          that the task that Arthur has here is a  
20          difficult one.

21                     So I think, while the notion of  
22          NIH acting in some kind of coordinated

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1 capacity is fair enough, there is a much  
2 bigger issue of what we do with the very large  
3 amounts of money, and the Cancer Institute  
4 alone probably has a billion dollars or more  
5 that is devoted to activities in this domain.

6 I think a lot of the conversation  
7 here is precipitated by the question of what  
8 we should be doing with the CAN directive that  
9 is now before us. But it raises some very  
10 complex issues that my institute, in  
11 particular, faces, because we have got so many  
12 different things operating, which you will  
13 hear about from Jim Doroshow later on.

14 But Heart, Lung and Diabetes and AI all  
15 have the same set of issues. I think there is  
16 a kind of strong compulsion for us now to  
17 think about new ways for us to work with  
18 industry. We think that the game has changed,  
19 as Dr. Baum's comments indicated earlier.

20 MEMBER FAUCI: So, Harold, thanks.

21 That was really the point I was  
22 trying to make about how we can best work with

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1 industry.

2 CAN is a \$50 million issue. If it  
3 grows, and it grows while the NIH doesn't  
4 grow, it's not going to necessarily be new  
5 money.

6 So what you have to look at is,  
7 what is going on? Harold mentioned the Cancer  
8 Institute. We have about \$1-plus billion in  
9 the arena that Harold was talking about.

10 In the new response that Harold  
11 played a role in with PCAST, when he was in  
12 PCAST, about how we respond to emerging  
13 infections and the development of new drugs,  
14 there were some recommendations made about  
15 medical countermeasures. In that, there are  
16 initiatives, for example, of \$33 million for  
17 that Concept Acceleration Program, \$170  
18 million for Jesse's regulatory science. So  
19 it's much, much bigger than CAN.

20 So I don't know, Arthur, how we  
21 are going to ultimately decide to address  
22 this, but perhaps it might be good to think in

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1 terms of, what are the multitudinous ways  
2 beyond CAN that we can and should interact  
3 with industry, for the reasons that I  
4 articulated before?

5 Because, getting back to what I  
6 said, we have all heard the problems that  
7 industry has in getting products. How can we,  
8 the NIH, work with you better than we have  
9 been? I would just submit that's the major  
10 issue.

11 MEMBER RUBENSTEIN: It certainly  
12 seems to be consistent with Francis' charge to  
13 the Committee to look much more broadly. The  
14 CAN seems to be the catalyst, but not the end  
15 of all the possibilities out there.

16 MEMBER VARMUS: I would just say  
17 that I agree entirely that the emphasis is not  
18 just how does NIH work with industry. How does  
19 NIH work with itself, get itself coordinated?

20 (Laughter.)

21 And actually, it means sharing  
22 things among institutes. Some of the things,

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1           some of the discovery units that now exist  
2           come out of the OD, the Common Fund. I think  
3           your committee has a real charge here to try  
4           to figure out how the various components of  
5           the NIH enterprise, OD-funded elements that  
6           are involved in drug discovery, the Clinical  
7           Center, which is probably going to end up  
8           under the OD, and the institutes, which have  
9           their own programs in the drug development and  
10          clinical trials, make a more powerful whole.

11                   CHAIR AUGUSTINE: Yes, I would just  
12          like to observe, being one at this table who  
13          lives in a kind of different world from most  
14          of you, I think that the impact of DARPA,  
15          which has a very tiny budget compared to the  
16          total defense research and development budget,  
17          but it has an enormous, disproportionate  
18          impact because of certain features it has,  
19          such as investing in high-risk, high-payoff  
20          research or translation, which it does.

21                   Another model I wanted to mention,  
22          which you probably are familiar with, is

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1 Semtech from the semiconductor industry,  
2 which, as it happens, had \$50 million a year  
3 provided by the government back when \$50  
4 million was a lot of money.

5 (Laughter.)

6 And the model there was one for  
7 pre-competitive research, sharing the  
8 research, so every company wasn't duplicating  
9 what everybody else was doing. So that when  
10 something failed, everybody knew it failed,  
11 and they didn't continue on pursuing it  
12 themselves.

13 They had an oversight board that  
14 had government members on it who were  
15 legitimate scientists themselves. The  
16 government contributed scientists, as did  
17 private companies.

18 And it just strikes me that there  
19 are a couple of models out there that we might  
20 learn from.

21 MEMBER BRODY: Was the  
22 semiconductor effort a success?

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1 CHAIR AUGUSTINE: I think, by and  
2 large, it was. Yes, it is controversial, but I  
3 would say that I think the majority of people  
4 would say it was, in balance, successful.

5 MEMBER BRODY: We're getting  
6 towards the close, the end of the first  
7 session, but we're just beginning this  
8 discussion, which goes not only for a day and  
9 a half, but will probably go much further and,  
10 as you heard, is much more extensive.

11 One of the things that I throw out  
12 in jest, one of my favorite books is a book  
13 called *Moneyball*. It's ostensibly about  
14 baseball, but it's really about how to manage  
15 uncertainty.

16 And if you think about drug  
17 development, it's about the same as developing  
18 an MVP where, if you hit the ball three out of  
19 ten times, you're an All-Star.

20 And it strikes, when I talk to  
21 people in the pharmaceutical industry, that  
22 they don't have a good handle on why things

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1 fail, and that there probably isn't a more  
2 optimal strategy.

3 Right now, drug development is run  
4 by a group of insiders. We all grew up in the  
5 same way. We all believe our own dogma. But I  
6 think that there are other strategies that one  
7 might consider to optimize outcomes.

8 I think what we should do now is  
9 to give the panelists an opportunity to make  
10 one last comment in this session, not the last  
11 comment for the meeting.

12 But we'll just start with Jesse on  
13 this end. Don't feel compelled to say  
14 anything.

15 DR. GOODMAN: I think this is a  
16 very good discussion. One comment, it's not  
17 some concluding comment, but in terms of I do  
18 think, if you consider at NIH using some of  
19 these resources to build in certain areas,  
20 like training, I would think about how you do  
21 it in terms of starting to change the paradigm  
22 in the groups of people.

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1                   For example, I think if you just  
2                   put more training programs into academia but  
3                   don't sort of bring other partners into that  
4                   training, it won't have much impact. That's  
5                   one example.

6                   So perhaps there should be a  
7                   training program around product development  
8                   and evaluation, or whatever. That would also  
9                   include rotations in industry, at FDA, et  
10                  cetera, to really start getting people who can  
11                  think across a much more complex universe than  
12                  it used to be.

13                  The other comment on information.  
14                  I share with Rob the feeling that there is a  
15                  tremendous amount of information out there,  
16                  whether it's the basic discoveries that Tony  
17                  alluded to that we're not taking advantage of  
18                  or it's just the experience ever single day in  
19                  the hospitals and clinics in the United  
20                  States, or the experience in every clinical  
21                  trial which, as I said, we're never looking at  
22                  again.

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1                   So I think investing -- and NIH  
2                   has made some real contributions here --  
3                   investing in working with us and others in  
4                   building information platforms that can begin  
5                   to let us use this information, we're really  
6                   not doing it.

7                   But, again, I think we have to do  
8                   it differently. I think we have to create a  
9                   generation of people who have common sense and  
10                  understand clinical medicine, but also  
11                  understand information. These are like ships  
12                  passing in the night.

13                  You know, there is a similar thing  
14                  with epidemiology and medicine, where people,  
15                  if the p-value is .05, boy, as far as they're  
16                  concerned, it's true, even if I can look at it  
17                  and say this makes absolutely no sense.

18                  So, we somehow need to bring that  
19                  discipline, informatics and biomedicine,  
20                  together. Maybe it's too much for humans to  
21                  contemplate, but I think it's worth trying.

22                  MEMBER KATZ: Mary?

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1 MS. WOOLLEY: Rather than trying to  
2 derail the conversation toward public  
3 engagement, which is coming up, I know, as  
4 another panel, which I can't be here for, I am  
5 just going to give some thoughts to colleagues  
6 who will be there. So I will pass right now.

7 MS. SELIG: I guess what I would  
8 say is this idea of -- and I want to support  
9 what Greg sort of led us to in this  
10 conversation, that \$50 million is significant,  
11 and for most people very significant, when you  
12 get outside of the government structure.

13 But if it's just used to create  
14 another program that's not a catalyst for  
15 something bigger, which is where the  
16 conversation started to go, about getting  
17 outside the normal boundaries in NIH, and to  
18 the extent that organizations such as ours can  
19 be helpful and can be involved in those  
20 conversations, I think we would welcome an  
21 invitation.

22 The only other thing I wanted to

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1 say, I didn't get a chance to say before, but  
2 with regard to subsets of patients, both  
3 within diseases, but also among diseases. So,  
4 we have a particular type of cancer in our  
5 name, but the learning that's starting to  
6 happen about pathways is leading us to think  
7 about how can we work with other types of  
8 cancers. Maybe it's a breast cancer and a  
9 melanoma, but maybe there is some way that we  
10 can work together on a pathway and getting us  
11 outside of our sort of narrow focus.

12 And I do think that that is  
13 something that NIH can help the community  
14 with, getting out of that sort of traditional  
15 mindset. So, I would encourage that.

16 DR. PERAKSLIS: To probably  
17 supplement our comment with what Dr.  
18 FitzGerald said, one thing that has occurred  
19 to me is we have talked about drug discovery  
20 costing more in the last 20 years. We haven't  
21 actually talked much about why.

22 It's not because of people,

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1           because there's far fewer people doing it  
2           today, which I think is real important. So the  
3           point about we need to bring in excellent  
4           folks is important.

5                     The other thing that goes into  
6           that cost, and I am an informaticist, is  
7           technology. I think when we talk about why  
8           things work or not, if we're being data-  
9           driven, but data-driven means we're really  
10          being technology-driven versus hypothesis-  
11          driven, there may be an opportunity for  
12          balance there.

13                    I mean, one of the things I like  
14          to say as someone who does this, cancer is not  
15          intimidated by next-generation sequencing.

16                   DR. FITZGERALD: I will say very  
17          little except one thing. The daunting numbers  
18          in terms of the cost of drug development tend  
19          to tear at new initiatives to move to a new  
20          model.

21                    But, as we saw nicely this  
22          morning, most of that cost is the failure of a

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1 model that we know is unsustainable. So  
2 building in the price of failure of a failed  
3 model should not deter people from undertaking  
4 a radically-new approach to drug discovery and  
5 development.

6 MEMBER KATZ: Thank you.

7 Dr. Duncan?

8 DR. DUNCAN: I don't have a lot to  
9 add, but just one reflection. Years ago, in my  
10 previous life when I was in industry, in  
11 looking at sort of programs jointly between  
12 industry and NIH, there were some efforts in  
13 the infective disease space. It was actually  
14 quite hard for us as a company to think about  
15 how we would get involved in them, just  
16 because of the way they were designed. And  
17 they weren't designed in a way that gave us  
18 the flexibility to move where we really need  
19 to move from a drug development perspective.

20 So I would just say, if you are  
21 thinking about ways to try to increase the way  
22 that the industry and the rest of the

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1 community works better together, get the  
2 stakeholders together before you sit down and  
3 design the program to make sure everybody can  
4 really make a contribution.

5 And even sometimes industry can  
6 make interesting contributions. Something was  
7 mentioned just toward the end there around  
8 learning from failures. And in industry, you  
9 know, if a project fails, you've just got to  
10 move on. You've got to move on to the next  
11 project.

12 There is an opportunity cost to  
13 going back and investigating why something  
14 didn't work. Yet, there is often really  
15 interesting questions with the tools that are  
16 available from that project, but they never  
17 see the light of day because, again, the  
18 information never gets into the public domain.

19 So, again, taking information  
20 that's been gained in industry, taking it into  
21 the public domain, using that to really, then,  
22 teach you how to do it much better the next

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1 time would, I think, be helpful.

2 MEMBER KATZ: Thank you.

3 MR. BERGER: I have two thoughts.  
4 One is an observation that I learned today.  
5 This organization does fabulously well when  
6 they focus on a therapeutic area. I think of  
7 HIV. I think of what is happening in oncology,  
8 which has a surfeit of targets. I think of  
9 what is beginning to happen to hepatitis C. So  
10 when you choose a therapeutic area, you seem  
11 to be able to be very efficacious.

12 Another is -- a second point I  
13 want to make is from my own background. When I  
14 think of the NIH, I think of them talking to  
15 Merck or Pfizer or big behemoths. I live in  
16 the small world of biotechnology. There are  
17 about 560 public companies. There are probably  
18 400 or more private companies. I work with  
19 them. I very rarely hear the word NIH  
20 mentioned.

21 There may be 100 great biotech  
22 companies. Half of those are public; half of

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1           those are private. The word NIH is mentioned  
2           only when they talk about citations.

3                       I would love to see folks at the  
4           NIH involved on a personal level with some of  
5           these companies, and they would feel  
6           comfortable. Maybe a task force within the NIH  
7           based on a therapeutic area, exploring what's  
8           happening in the private sector, would be  
9           useful.

10                      Thank you for my invitation.

11                      MEMBER KATZ: Dr. Baum?

12                      DR. BAUM: Yes, I think others have  
13           mentioned the incredible value of information  
14           exchange and that collaboration in a pre-  
15           competitive way. I think that's something that  
16           the NIH should be very strong and active.

17                      And exchanging negative data or a  
18           forum for exchanging negative data is also  
19           very interesting because most people, you  
20           know, there's not a lot of journals that want  
21           to publish your negative data and things like  
22           that.

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1                   So, how do we get that more  
2 exposed? I think that's another thing that  
3 possibly an institution like this could help  
4 with, because I think that's very valuable  
5 information of why things fail, and we seldom  
6 pay much attention to it. So, I think that is  
7 very valuable.

8                   And I think, also, the role,  
9 helping to bring together the FDA and public  
10 companies is also a very interesting one,  
11 because a true collaborative environment is  
12 needed, I think, to advance things more  
13 quickly and to create a better understanding  
14 of the projects more quickly on both sides.

15                  So thanks.

16                  MEMBER KATZ: Well, again, I wanted  
17 to join Bill and others in thanking you all  
18 for being here. I know that some of you  
19 altered your plans considerably.

20                  This is really only the beginning  
21 of the conversation of how the NIH should  
22 really configure itself in terms of moving

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1           therapeutics with some greater celerity and  
2           facility.

3                       So I'll close by thanking you  
4           again, and by asking Amy to give us any  
5           groundrules that we need to know about in  
6           terms of reconvening, et cetera.

7                       EXECUTIVE       SECRETARY       PATTERSON:  
8           Thank you, Steve.

9                       Again, many thanks to all the  
10          panelists. I know you moved heaven and earth,  
11          some of you, to be here, and we're deeply  
12          grateful, and certainly hope that you can stay  
13          for the rest of today and into tomorrow, if  
14          possible. We'll adjourn now for a luncheon  
15          break and reconvene at one o'clock here in the  
16          room.

17                      Members of the Board, you have  
18          lunch, a box lunch, provided in the room just  
19          out, down the corridor.

20                      And for others, there is a  
21          cafeteria here on the first floor.

22                      Please come back by one o'clock.

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1                   And also, the panelists, you, too,  
2                   have your lunch here as well.

3                   (Whereupon, the foregoing matter  
4                   went off the record for lunch at 12:27 p.m.  
5                   and went back on the record at 1:12 p.m.)  
6

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1                   A-F-T-E-R-N-O-O-N   S-E-S-S-I-O-N

2                                           1:12 p.m.

3                   CHAIR AUGUSTINE: Good afternoon,  
4 everyone. I hope you enjoyed your lunch. We  
5 are ready to begin the second phase of the  
6 discussion of TMAT.

7                   Arthur, do you want to introduce  
8 this part of it and carry on?

9                   MEMBER RUBENSTEIN: I'm getting  
10 more and more jobs here.

11                                       (Laughter.)

12                   Francis, do you have a position  
13 for me here?

14                   CHAIR AUGUSTINE: Let's see. Here  
15 it says I'm supposed to say, "Great, I would  
16 like to turn our attention to...."

17                                       (Laughter.)

18                   It says, "Arthur, would you like  
19 to take the reins again?"

20                                       (Laughter.)

21                   I think that's the wrong reins,  
22 though.

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1 (Laughter.)

2 MEMBER RUBENSTEIN: Yes, Norm, I  
3 will.

4 (Laughter.)

5 I don't think that's helpful. For  
6 me to read Norm's comments is not that  
7 helpful.

8 (Laughter.)

9 All right. Somebody is rescuing  
10 me.

11 All right. On a more serious note,  
12 to build on this morning's program, I think  
13 it's obvious it's very tough and challenging,  
14 but I think everyone is trying hard to think  
15 about how to do it. I think that's very  
16 encouraging.

17 So, this afternoon we are going to  
18 really try to focus again on particularly what  
19 role the NIH specifically can play in  
20 translational medicine and therapeutics,  
21 related but not exclusively linked to the CAN  
22 itself or only that.

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1                   And in this regard, we have two  
2                   speakers, one a very good colleague of mine  
3                   who every day teaches me a lot of things at  
4                   Penn, and I'm delighted he's here, and then  
5                   another colleague, Mary Disis, who will also  
6                   talk.

7                   And the topic is Identifying a  
8                   Role for NIH: Lessons Learned from Academic  
9                   Health Centers.

10                  First will be Garret FitzGerald,  
11                  who is the McNeil Professor in Translational  
12                  Medicine and Therapeutics and Associate Dean  
13                  for Translational Research at Penn.

14                  Garret?

15                  DR. FITZGERALD: Thanks very much,  
16                  Arthur. Thank you to the committee for  
17                  inviting me to come along and talk to you  
18                  today. I will try to stick to the assignment.

19                  So, as came up in our discussion  
20                  earlier this morning, I think we're moving to  
21                  a more modular approach to drug discovery and  
22                  development. Classically, we've been used to a

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1 vertically-integrated pharmaceutical company  
2 that does everything. We are in the process of  
3 watching the disintegration of that model,  
4 currently, during the outsourcing phase of  
5 that model, but really the disintegration of  
6 the classical integrated pharmaceutical  
7 company model.

8 The biotech sector has been  
9 focused particularly on target identification,  
10 some proof-of-concept, and some investment in  
11 drug-ability. Whereas, the academic effort has  
12 been traditionally in target ID and a little  
13 proof-of-concept in model systems and so on.

14 And I think we're moving to this  
15 more sort of modular approach, where teams can  
16 assemble, different teams in different places  
17 and in different sectors, to respond to  
18 different challenges with respect to drug  
19 development. So the question is, how do we get  
20 there?

21 I might say that I think, to some  
22 degree, a realization of this type of model is

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1 beginning to emerge in the not-for-profit  
2 sector.

3 So, I think a big issue could be  
4 NIH's, if this is where we're going, how can  
5 we empower the academic sector to play a  
6 constructive role in this type of interactive  
7 modular approach to drug discovery and  
8 development?

9 So, why should we care? I think  
10 what we should try to do is, as I said,  
11 enhance the capacity of the academic sector to  
12 play, and, also, to enhance the ability of the  
13 academic sector to train interdisciplinary  
14 scientists in translational medicine and  
15 therapeutics. After all, it is in the academic  
16 sector that scientists are trained, and it is  
17 with the support of the NIH that this actually  
18 happens.

19 So, I've been in this game, I'm  
20 somewhat scared to say, more than 30 years.  
21 Thirty years ago, there were a few exemplars  
22 of departments of clinical pharmacology, and

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1 I've just mentioned a few of them -- the Royal  
2 Post-Graduate Medical School, Vanderbilt,  
3 Karolinska -- where clinical pharmacology as a  
4 discipline was a very sexy topic. It was a hot  
5 topic. It had charismatic leadership. And  
6 within these departments, these various types  
7 of pursuit were actually integrated within the  
8 same space.

9 And experts in mechanistic studies  
10 of drug action and using drugs as probes to  
11 understand physiology and disease, experts in  
12 pharmacokinetics and modeling, experts in use  
13 of proof-of-concept in model systems, what we  
14 now call systems pharmacology and physiology,  
15 the development of biomarkers, chemical  
16 biology, statistics and trial design, and  
17 toxicology all existed within divisions or  
18 departments of clinical pharmacology in a few  
19 places scattered across the world.

20 And that was a rich  
21 interdisciplinary environment which coincided  
22 with in some ways the Golden Age of Drug

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1           Discovery and Development.

2                       Now,       what       led       to       the  
3       disintegration of pharmacology, or at least  
4       that model of clinical pharmacology? Well,  
5       departments of medicine lost interest as there  
6       was a shift across centers. And what test can  
7       you apply in clinical pharmacology that can be  
8       billed for? None.

9                       And       pharmacology       departments  
10       tended to lose their way a little bit in the  
11       molecular era, part of the discriminate  
12       features that mark out a department of  
13       pharmacology from a department of physiology,  
14       a department of molecular biology, or  
15       whatever, in the molecular era.

16                      So I think, to some extent, some  
17       departments of pharmacology fused with  
18       physiology. Some disappeared altogether.

19                      Integrated curricula did no favors  
20       for the perception of pharmacology as a  
21       discipline. It was sprinkled like pixie dust  
22       across the length of an integrated curriculum

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1 and lost its identity as a discipline in many  
2 of our leading medical schools.

3 And this led to a reversion of the  
4 perception and, to some extent, the reality of  
5 clinical pharmacology as a discipline, back to  
6 rather boring pharmacokinetic studies, often  
7 in Phase I, based almost entirely in industry.  
8 So, clearly, this was unattractive for bright  
9 trainees.

10 So, I would contend that it's  
11 impossible to resuscitate the brand of  
12 clinical pharmacology. Essentially, it has  
13 served its purpose over time. So, if you want  
14 to resuscitate this sort of interdisciplinary  
15 skill set, it's impossible to do it under the  
16 banner of clinical pharmacology.

17 Now, of course, it's not just in  
18 science that we lose the ability to do things  
19 that we used to be able to do. So, when  
20 Brunelleschi was preparing his grant proposals  
21 for the guilds in Florence, trying to decide  
22 how he would portray the construction of a

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1 freestanding dome, he was faced with the  
2 problem that at that time in the Renaissance  
3 the way you built a dome was you built a mound  
4 of earth, you built a dome over it, and you  
5 scooped the earth out.

6 So what he did was he went south  
7 to Rome and he sat in front of the Pantheon  
8 for two months, which had been built in the  
9 1st century as a freestanding dome, to try to  
10 understand how it was done, so that he could  
11 recapitulate this expertise so many hundreds  
12 of years later.

13 So, as we discussed this morning,  
14 I think the lack of people who blend these  
15 various skill sets that I've described to you  
16 a couple of slides ago in their own experience  
17 has really come at a great cost to various  
18 parts of the pharmacokinetic industry for us  
19 in this country.

20 I think we have really paid a  
21 price for it in the understanding of  
22 prescribing physicians of the medicines that

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1           they prescribe. I think we have paid a big  
2           price for it in drug discovery and  
3           development, particularly in drug development.  
4           Because I would contend that the investment in  
5           drug discovery actually has been, to some  
6           degree, cost-effective, and the whole process  
7           has been revolutionized.

8                       And as was mentioned several times  
9           this morning, we have many potential drug  
10          targets. That's not really the issue. Where  
11          things really break down is in drug  
12          development.

13                      I think there's a big issue in  
14          terms of regulatory science, and that needs to  
15          get re-infused with these other elements of  
16          the discipline beyond, say, pharamaco-  
17          epidemiology.

18                      And, I think, undiscussed so far  
19          in this country is the absence of any input,  
20          never mind leadership, from expertise in  
21          pharmacology and the whole issue of  
22          comparative effectiveness.

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1                   So, what about the attempts of  
2                   redemption since the disintegration of  
3                   clinical pharmacology, as we used to know it?  
4                   Well, many of the elements have actually  
5                   matured as disciplines in their own right. So  
6                   we have seen the development of chemical  
7                   biology as a discipline. We have seen the  
8                   development of what's called systems  
9                   pharmacology.

10                   Last week I was out at NIGMS at a  
11                   meeting here, and systems pharmacology is an  
12                   attempt to fuse expertise in systems biology  
13                   with what is beginning to be called, in some  
14                   drug companies, translational pharmacokinetics  
15                   and pharmacodynamics. But for now, it is  
16                   really systems biologists, often with a  
17                   background in engineering or computational  
18                   science, traditional pharmacokineticists and  
19                   modelers, speaking different languages with no  
20                   integrative glue between the two and very  
21                   little understanding of human biology,  
22                   frankly, never mind human pharmacology,

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1 represented in either constituency, I would  
2 say.

3 Bioinformatics -- we have heard  
4 about it, and I'll come back to it.

5 Many drug companies have, quite  
6 understandably, recognized this challenge,  
7 have recognized the disintegration of this  
8 integrative glue, and have created a variety  
9 of structures over the last 20 years to try to  
10 address the problem.

11 It usually goes this way: you  
12 gather together some MD/PhDs. You brand this,  
13 according to the times, experimental medicine,  
14 molecular medicine, whatever, and you have  
15 these people superimposed on what is a  
16 conventional siloed structure of drug  
17 discovery and drug development.

18 You get them a little money, but  
19 relatively speaking, very little money, and  
20 then you expect them to be able to influence  
21 the behavior of the people in the traditional  
22 siloed elements of the process. And generally

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1 speaking, those structures have lasted three  
2 to five years.

3 CTSAs, Clinical and Translational  
4 Science, we'll talk more about that, but  
5 that's clearly been a big initiative of NIH.  
6 And the focus here that is relevant is on so-  
7 called T1 translation, the translation that  
8 straddles the translational divide, not to be  
9 confused with the translational further down  
10 the stream. But I ask you, who will flock to  
11 the banner of T1 translation?

12 So, other attempts of redemption  
13 are that part of the CTSAs' remit was a focus  
14 on education, and we're going to talk about  
15 the importance of training. The difficulty  
16 here is that clinical and translational  
17 research, as a term, encompasses a very broad  
18 constituency, from the most basic science  
19 through to health services research. It  
20 includes many developed disciplines, basic  
21 science disciplines, clinical epidemiology,  
22 health services research.

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1                   T1 translational research is the  
2 orphan without a name. And yet, in some ways,  
3 it is the most cardinal point of the process.

4                   The NIH, as Francis alluded to,  
5 has developed many relevant resources that are  
6 pertinent to this effort in terms of the  
7 translational mission, resources, and  
8 intrastructural access to, including the  
9 Clinical Center, which we have discussed this  
10 morning.

11                  And as well as that, as has been  
12 mentioned by several of the IC directors, many  
13 of the ICs themselves have developed programs,  
14 pitched out accelerating cures or translation.

15                  So, why can't we attract the best  
16 and the brightest of our medical students and  
17 our science undergraduates to get into this  
18 business? So, what brought any of us into what  
19 we wound up doing? It was usually charismatic  
20 leadership and the perception that this is the  
21 hot area of science.

22                  I remember when I came to Penn, if

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1           you'll pardon a local joke, I was staggered to  
2           find that, of the undergraduate students, 80  
3           percent of them were opting to major in gene  
4           therapy. I rest my case.

5                     All right. So, one of the reasons  
6           is that they can't see anything. They can't  
7           see a discipline that has an integrative  
8           mission and that has the resources and  
9           membership that render it visible. It's not  
10          perceived as a hot area. There are few  
11          training options pitched at this science.  
12          There's absolutely no career path, and there  
13          are no programmatic initiatives where they can  
14          see that these skills are actually core to the  
15          sense of the initiative.

16                    So what can we do and what can NIH  
17          do, and what can we do in academia? Well, I  
18          would say, first of all, we need to brand this  
19          discipline. I think, obviously, translational  
20          medicine and therapeutics is a great name. It  
21          captures the excitement of translation. It  
22          puts it at the heart of medicine. It says we

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1 are trying to discover new therapeutics.

2 I think we really need to adopt a  
3 unifying nomenclature. This effort has many,  
4 many different names, all of them really  
5 scattered across the landscape with very few  
6 adherents. We need to aggregate this effort  
7 under a unifying nomenclature.

8 As Francis mentioned, there are  
9 many initiatives, existing initiatives, funded  
10 initiatives, within the NIH that are pertinent  
11 to this, but they're scattered. And it's  
12 difficult to sort of even perceive them, if  
13 you're interested in this area, as aggregated  
14 within a tangible resource.

15 And similarly, within many of our  
16 academic institutions, there are many  
17 resources relevant to translational medicine  
18 and therapeutics, and they are scattered  
19 across the institution. They have not been  
20 aggregated under a visible brand.

21 I think we need to create training  
22 programs in TMAT. I think we have a big issue

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1 here that actually relies on coordinated  
2 efforts by both the NIH and institutions, and  
3 perhaps the NIH, having the funding stick, can  
4 drive the institutions to reform.

5 But this type of research takes  
6 much longer to do than the usual performance  
7 cycles that accord with a five-year funding  
8 period. And similarly, it takes much longer to  
9 do for a conventional assessment of progress  
10 within the timeframe that leads to promotional  
11 decisions within academic centers.

12 To give you an example, when I was  
13 training in the Hammersmith, if we wanted to  
14 address a question in clinical research, you  
15 would ask the people in the room, your other  
16 post-doctoral fellows, would they be willing  
17 to volunteer, and you would probably do it the  
18 next morning. To do the same study now, the  
19 lead time can be a year. I'm not saying it was  
20 better then, but I'm just saying that's a  
21 changed reality.

22 So, this is a very different type

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1 of science, particularly if you are trying to  
2 integrate both basic and clinical elements of  
3 this type of science. And I think we could  
4 couple training initiatives with programmatic  
5 initiatives that are actually reliant on TMAT.

6 So, let's talk about each of those  
7 issues in a little bit more depth. Why a  
8 unifying nomenclature? Because I think it's  
9 really important here that this should be an  
10 initiative that is coordinated across  
11 countries as well as across sectors. I  
12 mentioned earlier this morning that the  
13 Wellcome Trust has already had an initiative  
14 in this area. But right now, we have this sort  
15 of laundry list of different names for the  
16 same thing, which really fragments the  
17 exercise.

18 So, I think what's really  
19 important is that something like TMAT, I  
20 think, would brand the interdisciplinary  
21 integration of the knowledge, but not  
22 supplant, for example, particular expertise in

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1 chemical biology or in systems pharmacology.

2 One can fly under two flags, but  
3 what this really speaks to is the  
4 interdisciplinary integration of those forms  
5 of knowledge. It begins to create a common  
6 language.

7 Over the last couple of years, we  
8 were putting together a highly-  
9 interdisciplinary program around the  
10 personalization of medicine. And one of the  
11 things that became clear in the course of that  
12 time was that we spoke different languages. We  
13 actually meant different things when we said  
14 the same words.

15 It begins to foster structures in  
16 which experts in the distinct elements  
17 commingle. So that was one of the great  
18 strengths of what clinical pharmacology used  
19 to be. You actually had an organizational  
20 structure with space and laboratories where  
21 people whose expertise was in kinetics or  
22 statistics or toxicology and human biology or

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1 biology or large animal biology actually  
2 commingled with each other.

3 I think it's really important that  
4 this type of initiative should be aligned with  
5 initiatives in other countries, but also with  
6 approaches to the problem within industry.

7 And finally, I would say that  
8 regulatory science is the other side of the  
9 same coin. TMAT is the academic manifestation  
10 of a solution to the problem. Regulatory  
11 science is its complement in the regulatory  
12 domain.

13 So I think the attraction of  
14 clustering the resources in a structure is  
15 that it gives you a seat at the table. And  
16 indeed, in our experience, when we were  
17 forming the Institute many years ago now, that  
18 was exactly the objective, that there were  
19 scattered resources and people relevant to  
20 this effort who were invisible institutionally  
21 when it came to decision-making. The idea was  
22 really to aggregate those resources and to

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1           amplify them.

2                       So one approach to doing this  
3           within academic centers would be the  
4           following:

5                       First of all, one could have an  
6           institute like we do. Or, secondly, one could  
7           take advantage of the clinical and  
8           translational science institutes that are  
9           beginning to proliferate and have within them  
10          a center for TMAT. The attraction of that is  
11          that it's a home for basic, for clinical  
12          scientists, for all types of scientists that  
13          might be relevant to this.

14                      The attraction of an institute or  
15          a center is that it would be a home to a  
16          spatial and educational resource relevant to  
17          an initiative in this area.

18                      Now, as far as physicians are  
19          concerned, the number of them interested in  
20          this type of science is likely to be very few,  
21          actually. And you run into the problem that  
22          there might be one in endocrinology and three

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1 in pulmonary or two in cardiovascular. There's  
2 no critical mass.

3 So the attraction might be to have  
4 a divisional structure that actually straddled  
5 all the clinical departments, so that you  
6 picked up that two or three people in surgery  
7 and four or five in psychiatry, and you gave  
8 them a common home for clinically-qualified  
9 people who are interested in this type of  
10 discipline.

11 And then, finally, they might  
12 have, as appropriate, secondary appointments  
13 in basic science departments. And obviously,  
14 similarly, basic scientists who are interested  
15 in this might have secondary appointments in  
16 clinical departments.

17 So, that way, you take something  
18 that has a relatively small and scattered  
19 constituency and you give them an  
20 organizational home that also commands  
21 resources.

22 So this is not a controlled study,

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1 but, for example, when we did cluster and  
2 aggregate resources in that domain at Penn and  
3 it became very visible and a source of  
4 distributing resources, it became very  
5 attractive. This is just showing how dense the  
6 interactions became over time across  
7 departments following the institution of the  
8 institute.

9 So what about training programs in  
10 TMAP? Well, I must say, I favor a master's  
11 degree as a sort of introductory basal degree  
12 that gives you the interdisciplinary exposure  
13 and then allows you to begin to focus in the  
14 area where you're likely to develop your  
15 expertise. And obviously, that can be built  
16 out of the CTSA programs.

17 The NIH, through the CTSA  
18 initiative, as I'm sure we'll probably hear of  
19 in T1 translational research, will become a  
20 repository for distance learning in  
21 translational research and, clearly, could be  
22 readily integrated into that type of

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1 initiative.

2 I think it is important that, with  
3 any training program, there should be the  
4 option, not necessarily the compulsion, and we  
5 could discuss that, but certainly the option  
6 to rotate into industry, the FDA, and the  
7 Clinical Center. And the other option that I  
8 think we should really keep in mind is the  
9 fact that this is an international effort.  
10 There have been big initiatives in  
11 translational research in many of the  
12 countries in the developed world, and they  
13 each bring different things to the party.

14 I think for people who undertake  
15 that initial training, they need a career  
16 structure and they need a bridge vehicle in  
17 terms of funding. I think that one of the  
18 programs that is particularly attractive to  
19 help them to do that is a K99 type of program,  
20 where it covers some of your post-doctoral  
21 training into the early years of your junior  
22 faculty appointment.

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1                   But I think this issue of the fact  
2                   that it is a long training cycle and that  
3                   promotional structures need to be adjusted to  
4                   reflect that, is really important. And of  
5                   course, we've done that before. We did that  
6                   with the MD/PhD program.

7                   Okay. So I think, besides  
8                   training, one could have programmatic  
9                   initiatives that are coupled with training to  
10                  raise the profile of this type of endeavor.  
11                  One could use such a call to incentivize the  
12                  use of existing core resources and to actually  
13                  advertise them to the constituency, that they  
14                  exist, and to motivate them to utilize them.  
15                  And not the core resources that exist within  
16                  the NIH, but, for example, analogous core  
17                  resources that exist within the FDA.

18                  I think in this type of endeavor  
19                  what's really important is to allow for the  
20                  flexibility to utilize money to buy services,  
21                  because many of these services don't exist  
22                  within institutions. And in some respects,

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1 many of these services don't exist even in  
2 terms of what's been developed within the NIH  
3 so far.

4 So, for example, the types of  
5 things that I'm thinking about are toxicology,  
6 so-called blue-collar chemistry, the tedious  
7 but necessary confirmatory proof-of-concept on  
8 human primate studies, and in many schools,  
9 regulatory support.

10 I think what would be really nice  
11 in terms of a unifying nomenclature would be  
12 to actually adopt this brand for the many  
13 existing IC-based initiatives in the  
14 translational space, so that people begin to  
15 associate these things and think this actually  
16 is an area with momentum that I might be  
17 interested in training in.

18 And I think the other thing that  
19 is necessary in this business, where you  
20 really are competing with people in the real  
21 world as opposed to just in the academic  
22 world, is speed and flexibility beyond the

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1 conventional review cycles.

2 So, I'll end by talking about some  
3 larger issues which I think are opportunities  
4 for NIH leadership in this domain and that are  
5 necessary and fundamental to reforming this  
6 space.

7 We have talked about intellectual  
8 property. We've talked about the pre-  
9 competitive space. These discussions are  
10 beginning to occur on the other side of the  
11 Atlantic as well as here.

12 I think the NIH could play a  
13 really leading role in beginning to address  
14 these really outmoded approaches and  
15 expectations towards intellectual property  
16 that we have both in academia and in industry.

17 It's been talked about before, and  
18 I think this is absolutely fundamental. If you  
19 are to move to that sort of modular structure  
20 of drug discovery and development, the  
21 infrastructure on which that model is built is  
22 the ability to share information in a

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1 compliant and secure way, extremely  
2 heterogenous information, and to be able to  
3 integrate it and to include, obviously,  
4 clinical information as well.

5 And that's a sort of easy thing to  
6 say and an extraordinarily difficult thing to  
7 do. Again here, this is somewhere where the  
8 NIH at a 30,000-foot level could play a really  
9 important role.

10 Then, finally, I think this is  
11 another issue that surfaced this morning. That  
12 is the way the rules of the game are set by  
13 the regulatory agency. There are all sorts of  
14 contradictions in the way the rules are set  
15 right now.

16 So, for example, if you're  
17 developing a drug for use in arthritis, you,  
18 the sponsor, are positively disincented to  
19 explore the human biology, the human  
20 pharmacology of that drug, beyond the  
21 contextual setting of arthritis, until that  
22 drug is approved. There is a disincentive for

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1           you to do that because, if you, for example,  
2           explore cognitive functions and get a sort of  
3           potentially negative signal, that has to be  
4           reported to the FDA, and that is not something  
5           that actually incents you to do that.

6                       So, in the same way that we  
7           created a safe haven for pharmacogenetic  
8           studies, I think the regulatory agency can  
9           play a really important role in terms of  
10          creating a safe haven for systems  
11          pharmacology, but pre-clinically, but, more  
12          importantly, clinically, early in drug  
13          development.

14                      So, I think these regulatory  
15          incentives can really be relevant to a  
16          comprehensive exploration of drug action,  
17          innovation, and, indeed, early risk detection.  
18          It is here that TMAP bumps up against  
19          regulatory science.

20                      So, I think there are three areas  
21          on a larger scale where there's a real  
22          opportunity for the NIH to do something.

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1                   So my time is up, and I'll end  
2                   with a comment from one of my favorite  
3                   Dubliners, Oscar Wilde. He says, "It's a very  
4                   sad thing that nowadays there's so little  
5                   useless information."

6                   Thank you very much.

7                   MEMBER RUBENSTEIN: Thank you,  
8                   Garret.

9                   I think, just because we're  
10                  running a little late, I would like to take  
11                  the prerogative, if all of you agree, that we  
12                  ask Mary Disis -- is that how you pronounce  
13                  it? --

14                 DR. DISIS: Disis.

15                 MEMBER RUBENSTEIN: -- Disis, to  
16                  give her presentation, because it's related to  
17                  Garret's. Then we'll have some questions for  
18                  both of them after it, if you agree.

19                 Mary is going to talk about -- she  
20                  is the Co-Chair of the T1 Translational  
21                  Research Strategic Goal Committee, CTSA  
22                  Awards, University of Washington. She is going

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1 to talk about the same overall subject that  
2 Garret did, and then we'll have questions for  
3 both of them, if everyone agrees.

4 DR. DISIS: Thanks.

5 So my talk is going to be a little  
6 bit more practical, and it's going to  
7 emphasize tools and existing tools. I think  
8 one of the things that the CTSA program has  
9 really brought to bear is that there's a ton  
10 of already-developed resources for  
11 translational research, especially drug  
12 development, not only out in the community,  
13 but here at NIH. But they're just organized;  
14 in some ways, they're very outdated.

15 So technology and tools really  
16 drive science. That's what accelerates the  
17 pace of scientific discoveries. And technology  
18 and tools needed to advance a discipline can  
19 be physical -- I'll show you a few examples --  
20 methodological and educational, just as Garret  
21 talked about.

22 The generation of these type of

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1 transformational technology and tools in  
2 itself requires innovation, scientific rigor,  
3 expertise, and a culture change. So the  
4 development of these tools in themselves is a  
5 high-level scientific endeavor.

6 They are many examples of where  
7 technology really changed science and the  
8 science infrastructure and transformed  
9 intradisciplinary science within a discipline.  
10 So, for example, human genomics, I mean this  
11 is from *Nature*. They describe the big wins in  
12 human genomics. It's all around tools and the  
13 development of tools.

14 If you look at cancer biology, in  
15 the 1990s, the development of these mouse  
16 models transgenics to look at epidermal growth  
17 factor in knockout. You know, I'm an  
18 oncologist, so this is like the bread and  
19 butter for us. Or the study of HPV-related  
20 cervical cancers. There are actually mouse  
21 models now that almost completely recapitulate  
22 human disease.

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1                   This results in an explosion of  
2                   our understanding of cancer and biological  
3                   pathways that are feeding the development, but  
4                   very little of this has actually ended up  
5                   resulting in being used for models of  
6                   translation. So that's the reason why. Why  
7                   aren't these great tools not only being  
8                   extrapolated into T1 drug development in a  
9                   much greater way, but also why are these type  
10                  of tools being developed for T1 translational  
11                  research?

12                 Part of that is due to the very  
13                 big fact that translational research, instead  
14                 of being intradisciplinary, is really  
15                 multidisciplinary. So, there are many diverse  
16                 technologies and tools that are needed for T1  
17                 research that are held by different  
18                 stakeholders in silos. They are often  
19                 scattered.

20                 So, when you look at academic  
21                 institutions, these tools are located all over  
22                 the place. The CTSA program has taken a lot of

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1 resource in terms of trying to gather these  
2 tools all into one place, as Garret talked  
3 about before.

4 And until now, translational  
5 technology and tool development has not really  
6 been a priority. People have been doing one-  
7 offs, developing tools and leaving them to be  
8 used by small groups, not available to larger  
9 groups, many times because people don't even  
10 know about them.

11 Multidisciplinary research, again,  
12 requires a broad array of tools. The  
13 development of those tools often takes  
14 scientific collaboration of diverse  
15 disciplines. There has to be a team approach  
16 to resource development, and that's very hard  
17 when you're talking about resources. Everyone  
18 wants to hang onto their own resources.

19 And finally, translational  
20 research and discovery application requires  
21 active participation by the public. Before I  
22 got involved with the CTSA program, I never

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1 realized how big of a barrier that was. I  
2 mean, we always knew that enrollment in  
3 clinical trials is less than 7 percent or 5  
4 percent or 8 percent of people in populations,  
5 but translational science is not a public  
6 value. People don't realize the role research  
7 plays in creating the medicines that they use.

8 So you have these wonderful high  
9 throughput technologies for target  
10 identification, and then they get down when  
11 you get to biologic validation. And finally,  
12 by the time you hit clinical translation, you  
13 have a huge bottleneck, not necessarily  
14 because some of the most critical tools aren't  
15 there. It's just that they're not able to be  
16 accessed. And NIH has a lot of these tools  
17 available for that type of access.

18 Now, what I've learned is that the  
19 CTSA program has very unique focuses that can  
20 provide lessons learned. Certainly, on a  
21 national level, through the CTSA Consortium,  
22 they are providing a lot of lessons learned

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1 within regions and across the United States in  
2 terms of this individual program.

3 But I think that the CTSA lessons  
4 learned can provide some take-home messages to  
5 NIH and other very large organizations that  
6 are interested in accelerating T1 research or  
7 drug development.

8 So, first of all, the unique  
9 aspects of the CTSA program is that we  
10 actually had a mandate to do research about  
11 the translational research process. So the  
12 amount of data available within the CTSA  
13 program about what is needed or where the  
14 holes are is really vast and is in the process  
15 of trying to be organized.

16 We have a mandate to try to  
17 identify and solve barriers that we identify  
18 for the research in very innovative ways, to  
19 transform the environment, and take outdated  
20 technologies and bring them up to where they  
21 should be in terms of trying to make the  
22 pathway faster.

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1                   We       have       to       accelerate  
2       translational   science   technology   and   tool  
3       application,   make   sure   that   tools   are   being  
4       used   by   our   constituency.   That   means   we   have  
5       to   foster   team   science   and   eliminate   those  
6       silos,   break   them   down   in   some   way.

7                   And   finally,   I   think   this   is   one  
8       of   the   few   programs   within   NIH   where   we   have   a  
9       huge   mandate   to   engage   the   community   as  
10      partners.   This   is   a   big   holdup   in   terms   of  
11      getting   people   into   clinical   trials   or   people  
12      volunteering,   enrolling   their   newborn   babies  
13      in   being   able   to   be   followed   for   25   years,   so  
14      that   we   can   gain   understanding   about  
15      development   of   children.

16                  And   finally,   the   solutions   and   the  
17      lessons   learned   that   we   are   developing   in   the  
18      CTSA   have   to   be   transportable.   So,   if   we   can't  
19      take   what   we're   learning   and   give   it   to   you   as  
20      tools   that   you   can   use,   then   we   aren't   really  
21      doing   our   jobs.   And   it's   through   this   that  
22      potentially   we   would   be   able   to   take   these   big

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1 roadblocks away.

2 So, what I would like to do is  
3 give three examples. This isn't meant to be a  
4 high-level overview like Garret just gave, but  
5 drill down on just three of these things, of  
6 how you can see, and I am going to use  
7 examples from our CTSA, approaches to some of  
8 the barriers. Then, unfortunately, I am going  
9 to focus on the NCI, because that is what I  
10 know best, how some of the resources within  
11 NCI, let's say, could be retooled to become  
12 broader and accessible to lots of different  
13 people.

14 So, for example, we have to  
15 identify and solve barriers in innovative  
16 ways. One of the biggest problems that we  
17 tackled in the CTSA program was looking at  
18 clinical centers.

19 Clinical centers have been around  
20 for a long time in most institutions through  
21 the General Clinical Research Center Program.  
22 In the old days, what would happen is people

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1 would come in and they would be in the  
2 hospital for three days, and they would  
3 participate in clinical research. But that is  
4 not how clinical research has evolved now.

5 People come in as outpatients.  
6 Translational research is going on in the  
7 community. We need places where we can high  
8 throughput lots of people coming in for  
9 genomics studies and places where we can  
10 accept samples that can be picked up and taken  
11 to research labs.

12 Certainly, the CRCs were not very  
13 business-oriented. So they were really  
14 developed on an old model from decades ago  
15 that needed to come into the way clinical  
16 research is being utilized now.

17 So, many CRCs or clinical centers  
18 are using business tools to try to retool the  
19 CRCs. So, for example, one of the things we  
20 found in our CRC is that we had no idea what  
21 our capacity was, but the nurses were always  
22 busy.

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1                   We use Toyota Lean as kind of a  
2                   process to streamline some of these existing  
3                   resources. They're running all over the place.  
4                   It's taking patients three hours to have what  
5                   should be a very simple visit.

6                   In these type of business  
7                   processes, you create what is your ideal  
8                   state. The ideal state with all the  
9                   stakeholders in the room, what would you like  
10                  this to look like? Then you can map out what  
11                  that ideal state is.

12                  Once you take these complex  
13                  resources and map what they should be doing,  
14                  that allows you to break them off into  
15                  segments and tackle those segments. Instead of  
16                  trying to retool the whole resource, retool  
17                  parts of it at one time. That allows people to  
18                  get their heads around deconstructing enormous  
19                  structures, having that type of  
20                  transformation.

21                  By teaming up with the business  
22                  school and using these types of tools, we have

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1           been able to decrease nursing overtime costs  
2           by 40 percent -- this is like a quarter-of-a-  
3           million-dollar savings -- while maintaining  
4           the same number of patient visits.

5                       By streamlining processes, making  
6           everyone well aware of what they're supposed  
7           to be doing, we have been able to eliminate  
8           the administrative structure of the CRC. We  
9           have reduced the time of scientific review by  
10          over 50 percent. Their own review process was  
11          a major problem for investigators, kind of  
12          like IRBs. And we have been able to institute  
13          two new services during the time when we took  
14          a 40 percent reduction in the overall budget,  
15          just by streamlining the processes.

16                      So, if you look at, let's say, the  
17          NIH RAID program, that is a fantastic program.  
18          It is desperately needed in the community. But  
19          it's not very well-utilized. In fact, there  
20          was just a recent review of the RAID program  
21          and some of the perceived problems with the  
22          program.

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1                   When I read that review, it struck  
2                   me, it's almost identical to some of the  
3                   things that have been said about the CRC types  
4                   of reviews: slow application process, limited  
5                   users, slow manufacturing or slow throughput  
6                   in these clinical research centers, unclear  
7                   capacity, very complex outsources, and a lack  
8                   of awareness of the resource.

9                   So, many times these resources  
10                  have been developed; they have been started,  
11                  but they've never gone back and been retooled  
12                  for the usership. I think some of these tools  
13                  that are being developed in the CTSA program  
14                  would be very useful to make the resources  
15                  more high throughput.

16                 If you look at the CTSA program,  
17                 there's a lot of technologies at a lot of  
18                 institutions. They have come up through  
19                 multiple centers. People really want to use  
20                 them, and those that own them really want  
21                 people to use them, so they can keep the  
22                 resources going. But no one knows where they

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1 are.

2 Many CTSA's, ours being one of  
3 them, create a directory of technology  
4 resources. Our CTSA covers a very large five-  
5 state region in the Pacific Northwest.

6 Our technology resource directory  
7 has 135 shared resources from a five-state  
8 region linked with educational material, like  
9 streaming websites or lectures or information  
10 about how you use the resource, sample  
11 preparation, things like that, and live  
12 technology consulting via PhD-level  
13 scientists.

14 When this resource was developed  
15 and this is data collected on the website  
16 where this resource is, most of the hits a  
17 year after the resource started came from the  
18 University of Washington. Who would have  
19 known? But after a year, most of the hits now  
20 are coming from direct links that go directly  
21 to that technology resource. And the next  
22 highest number of links are coming from search

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1 engines outside the University across the  
2 United States, and 85 percent of those people  
3 go on to other web pages within our CTSA  
4 program.

5 During the time that this  
6 technology resource was launched, our  
7 membership grew 200 percent, just because  
8 there was such a need for people to get a  
9 handle on their technology. This is just a  
10 small part of a larger technology engine that  
11 is being developed within the CTSA program to  
12 link unique technologies at other CTSA  
13 institutions on a national level.

14 So, if you look at, again, NCI,  
15 they have an incredible, and NIH in general,  
16 amount of resources surrounding transgenic  
17 mouse models. When you look at that slide that  
18 I showed you about cervical cancer, and there  
19 is now a E6/E7 transgenic mouse where people  
20 can study the development of therapeutics for  
21 cervical cancer. Although that mouse was made  
22 in 1992, there have been 150 publications, and

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1 the vast majority of the number of biology-  
2 based still elucidating pathways that are  
3 modulated by viral oncogenesis. Not many  
4 translational researchers in this environment  
5 are using that most relevant mouse model for  
6 testing new therapies.

7 When you look at the NIH website,  
8 I just clicked on a couple of the consortia  
9 surrounding transgenic mouse models. I put  
10 dot, dot, dot. There's at least 10 more, much  
11 like these different types of resources for  
12 access to these transgenic mice. And many  
13 transgenic models that are being made in other  
14 institutes have direct relevance in other  
15 disease.

16 If NIH could just take their  
17 playing field of transgenic mouse models and  
18 get that to a greater usability, that would be  
19 an incredible resource for people in the T1  
20 area, and it would probably really increase  
21 their access to being able to move to the  
22 clinic faster.

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1                   And finally, I wanted to end with  
2                   engaging the community as partners. I play in  
3                   the T1 field, so I'm more laboratory-based.  
4                   Before I took a role in the CTSA, I never  
5                   really thought of this, except that when we go  
6                   into Phase I clinical trials, it takes five  
7                   years to enroll a 20-patient study.

8                   But, recently, this summer, we had  
9                   a summer workshop for high school science  
10                  teachers. These people self-identified, so  
11                  they are really into biology and science. They  
12                  came and spent a week and learned about  
13                  translational research. And of course, they  
14                  said, you know, marvelous things.

15                 But within all the marvelous  
16                 things they said, there were comments to me  
17                 that were really striking, like, "I never  
18                 realized how critical research is for  
19                 medicine." These are science teachers.

20                 "I wouldn't think a researcher  
21                 would be so caring, nice, and friendly." Or "I  
22                 always thought research was for extremely

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1 intelligent people who were socially inept."

2 (Laughter.)

3 You know, I laughed first. But,  
4 then, when I walked away from the presentation  
5 that showed me the comments, I thought, this  
6 is serious stuff. I mean, these were  
7 compliments to us about this. This is what our  
8 science teachers are thinking about research?  
9 They don't see the link between that.

10 And unless the public takes  
11 translational research as a value, we can do  
12 all we want with translational research, but  
13 we're never going to get rid of that  
14 bottleneck going into the clinic.

15 So, the CTSA's are interested in  
16 developing partnerships, meaningful  
17 partnerships, surrounding translational  
18 research. So, this is an example -- again,  
19 there's a bazillion examples in the CTSA  
20 program -- of WWAMI-based, this five-state  
21 area, taking clinical practices and making  
22 them a research network. It means giving them

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1 research capacity.

2 So we went in. We took seven rural  
3 practices, saw a lot of patients, gave them  
4 data warehousing, put a team in there to help  
5 them address questions they were interested  
6 in. They had a townhall meeting, decided they  
7 wanted to study, based on what their patients  
8 wanted, do women taking teratogenic drugs use  
9 contraception? And what they found was they  
10 didn't and, moreover, we have no evidence that  
11 we ever told them that they should.

12 Now, when they finished that  
13 study, which not only are they publishing as a  
14 rural health network, but they are presenting  
15 at national meetings, it really transformed  
16 them. It's transforming their practices. It's  
17 making their patients feel that they got  
18 something out of this.

19 And these research practices now  
20 are coming saying, "We're really interested in  
21 being full members. Can we do clinical trials  
22 out here?"

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1                   This is the type of meaningful  
2                   interaction that NIH could have a leadership  
3                   role around, much like Garret says. So, for  
4                   example, when you look at the NIH website and  
5                   community, there's lots of stuff, numerous  
6                   programs for the community. They're all over  
7                   the place. There is little unification about  
8                   them, and there is no common mission  
9                   whatsoever.

10                  Many programs, even within  
11                  themselves, when you read about them, you're  
12                  not quite sure what NIH is trying to get out  
13                  of them. Many are superficial.

14                  There really is a need for a  
15                  cohesive plan to galvanize community support  
16                  in translational research in many ways, and  
17                  there's a need for leadership. Certainly, in  
18                  cancer these are successful programs on a much  
19                  smaller scale, but the Army of Women project  
20                  led from the National Breast Cancer  
21                  Coalition -- these are programs that have  
22                  really brought to bear women going into

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1 clinical trials in great numbers. And I think  
2 that there are some lessons to be learned from  
3 what's outside.

4 So, at the end of the day, the  
5 CTSA has developed many best practices and has  
6 a lot of lessons learned. NIH should use it as  
7 a resource as they go through this process of  
8 trying to figure out how they can play and  
9 have leadership in the T1 arena, especially  
10 because so many resources exist here that are  
11 not organized and not available.

12 These resources could contribute  
13 greatly to translational science if they were  
14 catalogued appropriately, if they weren't left  
15 in silos, and if they were operating a little  
16 bit more efficiently.

17 Evaluate the data collected in the  
18 CTSA program to assess potential new resources  
19 for development. There has been a huge  
20 national push on data collection in this area,  
21 and it would be great not to reinvent the  
22 wheel.

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1                   And also, encourage intramural  
2                   integration around translational science.  
3                   Bring those resources together, not within  
4                   NIH, but also intramural participation with  
5                   the extramural community in this T1 arena.

6                   And finally, ending with Garret's  
7                   slide, it's the major thing. You have the  
8                   national leadership, not only in community  
9                   integration, but in branding translational  
10                  research and drug development, T1 research in  
11                  general. You have the voice. You need the  
12                  vision. We will follow and back up that vision  
13                  and really galvanize the nation around this  
14                  area. That's the only way they'll get the  
15                  medicines and new personalized healthcare that  
16                  they are so interested in, but there is a very  
17                  big disconnect.

18                  So utilize the CTSA program, and  
19                  there's a lot of stuff in there that's sitting  
20                  there that we want to give out.

21                  MEMBER RUBENSTEIN: Thank you very  
22                  much, Mary and Garret.

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1                   What we are going to do, in the  
2                   interest of time, is have five short  
3                   presentations from people from within the NIH,  
4                   five minutes each. Then we will have a general  
5                   discussion involving them and Garret and Mary.

6                   So why don't we start with Jim  
7                   Doroshow, who is Director, Division of Cancer  
8                   Treatment and Diagnosis at NCI?

9                   We'll try to keep it to five  
10                  minutes each, if that would be acceptable.

11                  DR. DOROSHOW: Thank you very much  
12                  for the opportunity to present to this group.

13                  I wanted to talk to you about what  
14                  has gone on in the NCI's drug development  
15                  program, which, as many of you know, is  
16                  actually 55 years old, and as of the last few  
17                  years, is clearly showing its age.

18                  So, we have made a lot of changes  
19                  -- I'm going to share some of them -- that  
20                  really go the entire range, from looking at  
21                  different ways to do early drug discovery  
22                  through changing our early-phase clinical

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1           therapeutics program, looking at how to  
2           improve our delivery of biological agents as  
3           well as small molecules, and how to do  
4           clinical trials more effectively.

5                       So, this is a list you're not  
6           meant to read every line of, but, in fact,  
7           everything in black the NCI has been doing for  
8           some years and providing as resources to the  
9           experimental therapeutics community in the  
10          area of cancer. What we were not doing, and  
11          not doing very well, was providing medicinal  
12          chemistry high throughput screening and  
13          chemical biology resources.

14                      So, about two years ago, we began  
15          a planning process to change that particular  
16          deficiency to develop something we called the  
17          Chemical Biology Consortium. This was to be,  
18          and is -- it went into operation about a year  
19          ago -- an actively-managed group, a consortium  
20          of investigators across the country. So that,  
21          instead of the NCI supporting this activity by  
22          hiring a bunch of chemists, we went out and

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1 did a competition to try to find individuals  
2 who wanted to work together in teams to help  
3 work on high-risk projects that were not the  
4 kinds of things that, for the most part,  
5 industry was used to working on.

6 This is a list of investigators  
7 and institutions that are participating in  
8 this activity. It is a very good group of  
9 chemical biologists with a variety of  
10 different kinds of skills.

11 What we do now, and we have  
12 started as of last September, is have a  
13 quarterly process in which people put in  
14 applications for resources now in any part of  
15 the pipeline. They can ask for resources to  
16 early-phase proof-of-concept, proof-of-  
17 mechanism studies. They can ask for a high  
18 throughput screen for medicinal chemistry.  
19 They can ask for pharmacology and toxicology.  
20 This is reviewed by an outside group of  
21 special emphasis panels, either in discovery  
22 or development.

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1                   Just to give you an idea, this is  
2                   our first year. We had close to 200  
3                   applications, most of them from academia and  
4                   not-for-profit, some from biotech companies.  
5                   Most of those applications were for early-  
6                   phase therapeutics. Our level of success is  
7                   around between 15 and 18 percent.

8                   These review groups are made up of  
9                   half from academia and half from industry, so  
10                  that we have people who are very skilled in  
11                  understanding the kinds of hurdles that need  
12                  to be overcome.

13                 And if I can spend a minute or  
14                 two, I will just give you a couple examples of  
15                 projects that are ongoing. One of the first is  
16                 a project in the area of metabolomics from Chi  
17                 Dang at Hopkins, a world authority in the area  
18                 of MIC biology who discovered that LDHA is a  
19                 critical downstream target, working with a  
20                 chemist overseas, found a group of malarial  
21                 inhibitors that are very effective in  
22                 decreasing the growth of MIC-driven lymphomas,

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1 but not very useful in terms of inhibiting the  
2 growth of non-MIC-drive pancreatic xenograms.

3 So, what we are doing with Dr.  
4 Dang is to develop an entire high throughput  
5 campaign to try to find a new scaffold for  
6 this particular target. And the key to this  
7 really, at least is my opinion, is that we  
8 have the chemical resources to do what he  
9 can't or it's not available at Hopkins, but he  
10 will provide the critical biological glue to  
11 provide the expertise in the area of the  
12 target that will work toward moving ahead.

13 In the area of development, we  
14 have for many years and continue to try to  
15 reproduce reagents and work out of our  
16 community, not only small molecules, but  
17 immunomodulatory molecules. This is a list of  
18 the top five compounds that the cancer  
19 immunotherapy community felt were critically  
20 important to move into the clinic.

21 We have produced clinical grade  
22 IL-15 and have an IND that has just been

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1 approved for the first study of that compound  
2 in man. Now we're producing IL-7. And to go  
3 along with the production of these clinical  
4 grade molecules, we have just established an  
5 immunotherapy network to do Phase I trials  
6 specifically with the compounds that we have  
7 produced.

8 The last thing I would like to  
9 show you is a compound, and it's something  
10 that I think that only the NCI and all of the  
11 NIH can do, is to focus on a compound that has  
12 little or no -- because it's very old and it's  
13 been repurposed -- intellectual property.

14 This is a compound,  
15 fluorodeoxycytidine, which binds to the  
16 active pocket of DNA cytosine  
17 methyltransferase 1. It was originally  
18 developed actually at Memorial Sloan-Kettering  
19 as a pro drug of thioracil. It's of no use in  
20 that capacity. But about 10 years ago, it was  
21 found to inhibit methyltransferase and  
22 activate differentiation.

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1                   This is a patient on a Phase I  
2                   study done at the Clinical Center, a woman  
3                   with breast cancer on a morphine drip when she  
4                   came in with a substantial amount of her liver  
5                   replaced by breast cancer disease and in the  
6                   skin, who had, essentially, a two-year  
7                   response to this compound.

8                   Really, it shows how you can make  
9                   things, provide them to the extramural  
10                  community, work with them -- and this is a  
11                  trial done both at the Clinical Center and in  
12                  a variety of our Phase I sites outside -- to  
13                  bring things that really would be very  
14                  difficult to do otherwise.

15                 This just puts you in a schematic  
16                 version, a list of our repopulated pipeline  
17                 based on our recent one-year history of trying  
18                 to bring things in from the extramural  
19                 community. I think it's really possible to do  
20                 things that are difficult to do, are high-  
21                 risk, and provide resources that are not  
22                 available to academic investigators.

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1 Thank you.

2 MEMBER RUBENSTEIN: Thank you, Jim.  
3 I thought that was an excellent presentation.  
4 So thank you, and I appreciate that you had to  
5 do it quite quickly, but the data was really  
6 great.

7 Then Susan Old, the Deputy  
8 Director of Therapeutics for Rare and  
9 Neglected Disease Program at NIH, if you would  
10 proceed for five minutes, please?

11 DR. OLD: Thank you. I will do my  
12 best to rush through this.

13 I have been asked to talk about  
14 two programs that we're involved with, the  
15 Chemical Genomics Center and the Therapeutics  
16 for Rare and Neglected Diseases, which you  
17 have heard a little bit about both this  
18 morning and this afternoon. So you have seen a  
19 lot of the pipeline.

20 Where NCGC sits is in the  
21 discovery, sort of this, the blue, and a  
22 little bit into the probe, and where TRND sits

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1 is from discovery through proof-of-concept in  
2 humans, which would be Phase II in the  
3 clinical trials.

4 So NCGC is an intramural program  
5 at the NIH. It was founded as part of the  
6 Molecular Libraries Program, which is high  
7 throughput screening program. We have about,  
8 actually, we're up closer to about 85  
9 scientists now.

10 We, through the Molecular  
11 Libraries Program, bring in collaborators.  
12 Most of them are extramural. A handful are  
13 intramural, and from foundations, research,  
14 and pharma.

15 Our focus is on rare and neglected  
16 diseases. We come out of this program, and I  
17 don't think you're going to hear much more  
18 about Molecular Libraries, but the purpose of  
19 Molecular Libraries is take targets that have  
20 been identified in academic centers or other  
21 centers and develop high throughput assays and  
22 screen them -- you've seen this picture

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1           several times now -- on our robots with a  
2           compound. We have several compound libraries.  
3           The Molecular Library, the Compound Library is  
4           about half a million small molecules.

5                     Then we also do a fair amount of  
6           time in assay development, screening  
7           informatics, and paradigm development and  
8           chemistry in this area.

9                     So the reason that we work, and  
10          just to talk a little bit about rare and  
11          neglected diseases, and this has been brought  
12          up many times over the morning, the human  
13          genome codes for many, many proteins.

14                    The well-understood proteins are a  
15          very small portion, and these are the drug-  
16          able targets that pharma goes after for the  
17          most part. All the rest of the genome and the  
18          proteome are much more difficult to target and  
19          much less well-understood because of that. So  
20          that's a neglected area.

21                    And the same you could say for  
22          diseases. The prevalent diseases in the

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1 developed world are the diseases that pharma  
2 generally tackles.

3 So prevalent diseases in the  
4 undeveloped world are neglected, and non-  
5 prevalent diseases in the developed world or  
6 rare diseases are also neglected. So these  
7 neglected areas and rare disease areas is  
8 where TRND and NCGC focus.

9 So we're disease-agnostic. We are  
10 not part of a mission of any of the  
11 categorical institutes. So we do a fair amount  
12 of probe discovery just for basic research for  
13 probing, for going back in and understanding  
14 the biology.

15 We are somewhat nearer the NIH  
16 with cancer/infectious disease. We haven't  
17 done a lot of cardiovascular. I'm not sure  
18 why. But these seem to be the ones that come  
19 to us through the Molecular Library Program.

20 So what we do is we're an  
21 intramural program. We consist of a lot of  
22 chemists, biologists, robotics, compound

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1 management, informaticians, and the vast  
2 majority, except for a handful like me, come  
3 from -- and actually, I did work in biotech  
4 for a while -- come from pharma in the biotech  
5 area. So these are people that are well-versed  
6 in drug development, and we're bringing them  
7 into NIH in sort of an academic-like setting.

8 So, NCGC, there is a huge number  
9 of programs under this umbrella of NCGC. So,  
10 the Molecular Libraries Program, we are a  
11 center. So, we have a grant as part of the  
12 Molecular Libraries Program, the Common Fund.  
13 We are a center in the NCI CMC program, and we  
14 get the NEXT grants to work on.

15 We have a large program in Tox21,  
16 which I think you've heard a bit about in  
17 playing a role in the Gulf spill. But we are  
18 mostly working in figuring out novel  
19 toxicology assays that are not model-based or  
20 cell-based.

21 We have an RNAi intramural  
22 program, or we support all of the intramural

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1 programs in doing high throughput RNA  
2 screening. We have a number of intramural  
3 collaborators. We are actively working with  
4 disease foundations, and we actively work with  
5 biotechs and pharmas. These are the different  
6 types of things that we do.

7 So, these are our areas. So, this  
8 is mainly where NIH has played before in  
9 clinical and basic research in target  
10 identification or understanding of the  
11 biology, the mechanisms, the pathways. You can  
12 term this as translation because you are  
13 certainly translating basic knowledge,  
14 understanding of the genome and the proteome  
15 into pathways and targets. The Molecular  
16 Library takes those targets, does high  
17 throughput screening, and that is what we do.

18 Then our next hope is to work in  
19 the Valley of Death here and move, as we are  
20 hearing a lot from our market research, going  
21 out and talking to BCs and pharmas, that  
22 really for rare and neglected diseases, to

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1 minimize, to reduce the risk, so it will be  
2 licensed, we are really going to have to go  
3 through proof-of-concept in humans.

4 So this is TRND. It's a  
5 congressionally-mandated effort. Our  
6 governance is by the Office of Rare Disease.  
7 We administratively sit in NHGRI. However, we  
8 pay our own rent. We pay for all of our  
9 utilities. We pay for all of the support staff  
10 NHGRI gives us.

11 We are intramural. The vast  
12 majority of our collaborators are in the  
13 extramural. You can enter TRND at sort of any  
14 stage along this pipeline.

15 So, our distinguishing features:  
16 we are setting collaborations and  
17 partnerships. We are an intramural program.  
18 This is not a service center. This is an in-  
19 exchange-of intellectual engagement.

20 We're building the laboratories  
21 and expertise infrastructure at NIH. We're out  
22 at Shady Grove by the hospital, where NCI is

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1 going to be joining us out there shortly. We  
2 are disease-agnostics.

3 The big part of TRND not only is  
4 to facilitate this pipeline, but to do the  
5 science of pre-clinical development. We talked  
6 a lot about the fact this morning that the  
7 successes and the failures need to get out to  
8 the public, so that they can begin to inform  
9 the next series of studies. So, we plan to  
10 spend a large portion of our time with our  
11 intramural scientists in the biology and the  
12 chemistry, the robotics, the analytical, in  
13 understanding the pipeline and what works and  
14 what doesn't.

15 In addition, we're doing  
16 technology and paradigm development. We need a  
17 new process. We can't just repeat what pharma  
18 is doing. It fails 98 percent of the time or  
19 99.8 percent of the time. We don't want to  
20 recapitulate that. We want to improve on that.

21 Then we are involved, actually,  
22 with speaking some with Pfizer and some with

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1 some other groups; large-scale systematically  
2 purposing. We do the same list that you have  
3 seen from a number of other people. We do them  
4 in-house, or we are going to do them in-house.

5 So, we started in May 2009. We  
6 received our second funding in June of, I'm  
7 sorry, 2010, this year. We, like everyone  
8 else, are waiting for the budget to be  
9 approved to the recommended. The President's  
10 recommended was \$50 million.

11 We are going to, even though we're  
12 intramural, we're going to solicit for our  
13 collaborative projects. We are going to use  
14 the same process that NEXT uses, because it's  
15 a very similar process. We're just bringing  
16 things in-house.

17 So there will be a solicitation  
18 out in about two weeks. Projects will come in.  
19 It will have an external review. It will go  
20 through a series of secondary reviews,  
21 including the trans-NIH group that we have.  
22 And we will, hopefully, be able to fund,

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1 depending on the funds, three to five projects  
2 to get started. Then we hope that our labs are  
3 fully functional by fiscal year `12.

4 These are the pilot projects where  
5 we're piloting the pipeline. You can see they  
6 cross rare and neglected diseases, all  
7 different kinds of pathologies, intramural,  
8 extramural, nonprofit.

9 We are working with SOAR for the  
10 Niemann Pick disease and several other  
11 nonprofits. They're all at different stages  
12 and different kinds of compounds. So we're  
13 testing all the parts.

14 So the main thing, as you're  
15 thinking about NIH intramurally and  
16 internally, and where to go with sort of the  
17 overall collaboration, we have learned a lot  
18 in just the pilot projects that we have done  
19 in the last six months.

20 How do we get funding to our  
21 collaborators? We're intramural, not  
22 extramural. That's been an interesting

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1 challenge. Collaborative agreements, CRADAs,  
2 MOUs, non-CRADAs, CRAs. How do we do this in  
3 terms of intellectual property? The government  
4 has certain rules about what our intramural  
5 scientists do and where they contribute. And  
6 then how do we partner that with the outside  
7 world?

8 Project management, our advisor  
9 group so far has told us this is the No. 1 key  
10 thing we need to focus on in how we move these  
11 projects along, keep them on task; go/no-go;  
12 hitting our milestones, and turning over  
13 projects that are not working well and moving  
14 them into the more science discovery realm of  
15 why isn't it working.

16 We have discovered huge expert  
17 advice on NIH campus. I can't tell you, in  
18 talking to people -- I've been to huge numbers  
19 of institutes, as have my colleagues. There's  
20 great stuff going on inside intramural, in the  
21 extramural side, as well as out in the pharma  
22 and the BCs. Everyone we're talking to is very

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1 excited about this program and seeing what NIH  
2 can do. It is sort of a small start of the  
3 intramural, but partnering with the outside,  
4 how do we tackle some of these problems?

5 So, I think that's it, and thank  
6 you.

7 MEMBER RUBENSTEIN: Thank you,  
8 Susan. We appreciate that.

9 Now we'll turn to Thomas Miller,  
10 Program Director, Office of Translation  
11 Research, Institute of Neurological Disorders  
12 and Stroke.

13 Tom?

14 DR. MILLER: The purpose of the NIH  
15 RAID program is to provide an opportunity for  
16 investigators to advance promising candidate  
17 therapeutics forward in the pre-clinical  
18 development pathway, particularly if a  
19 roadblock has been encountered to further  
20 development.

21 The application of critical  
22 development resources after the selection of

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1 an optimized clinical candidate can help  
2 projects move quickly to IND when alternative  
3 sources of support can be really very  
4 difficult to identify.

5 Those of us working in this  
6 program are truly very excited about it. It  
7 fills a very important gap in the efforts that  
8 are underway outside the pharmaceutical  
9 industry to bring promising, effective  
10 candidate therapeutics to patients.

11 Successful applicants gain access  
12 to government expertise and therapeutics  
13 development and government contract resources  
14 to complete specific tasks in the pre-clinical  
15 development pipeline. No funds are awarded to  
16 applicant organizations. Currently, not-for-  
17 profit organizations and small businesses that  
18 meet the eligibility criteria for the NIH SBIR  
19 program are eligible to apply for support.

20 NIH RAID provides services for a  
21 broad set of potentially therapeutic agents,  
22 including small molecules, gene vectors, and

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1 proteins. These services include product  
2 development planning, research grade NGMP  
3 manufacture, formulation, pharmacokinetic and  
4 ADME studies, IND-directed toxicology, and  
5 manufacture of a GMP clinical supply.

6 The program is led and managed by  
7 a central office that is currently at NINDS.  
8 Jamie Driscoll from NIMH and Tony Jackson, the  
9 NIH RAID Program Manager, are very important  
10 members of this office.

11 Our scientific staff is currently  
12 at NCI. Jim Craddock and Pramod Terse, along  
13 with a number of NCI staff, provide not only  
14 leadership, but also an enormous amount of  
15 expertise to this part of the program effort.  
16 This scientific team not only plans projects,  
17 but also implements them and manages the  
18 performance of the contractors.

19 Our project team and its  
20 subcommittees have been integral to our  
21 relationship with the institutes and centers  
22 at NIH and access to the disease-specific

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1 expertise at those ICs.

2 We have accessed contract  
3 resources at NCI, NHLBI, and the TRND program.  
4 And our senior oversight from Dr. Katz, Dr.  
5 Landis, and the NIH Office of the Director,  
6 has been very supportive and helpful.

7 This is our project team, which  
8 currently has representatives from the 13 NIH  
9 ICs. This has been a truly trans-NIH effort.  
10 This team has been active and involved in the  
11 development, implementation, and growth of the  
12 program.

13 We established a process for  
14 consideration of NIH RAID projects that begins  
15 with electronic submission of applications  
16 using the X01 resource access mechanism. These  
17 projects are about \$2 million in total cost  
18 each on average.

19 Applications that are responsive  
20 to the NIH RAID scope are reviewed by CSR and  
21 receive a priority score. If an application is  
22 scored in the excellent or better range in

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1 peer review, we hold a meeting with the  
2 investigators, NIH RAID staff, and IC disease  
3 experts to formulate a development plan to  
4 advance the candidate therapeutic.

5 This meeting provides an  
6 opportunity to combine the expertise and  
7 experience of all the participants and leads  
8 to the development of final tasks, timeline,  
9 milestones, and budget for a project.

10 It's the flexibility of this  
11 process that enables NIH RAID to develop  
12 project plans that both maximize the chance of  
13 the candidate reaching the clinic and optimize  
14 the application of federal funds.

15 Then, after considering scientific  
16 input from the NIH disease experts, the  
17 Planning and Evaluation Subcommittee of the  
18 NIH RAID Project Team develops a funding  
19 recommendation, and that is submitted to the  
20 NIH Office of the Director for approval.

21 So far, the program has approved  
22 23 projects, 11 of which have been completed.

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1           These approved projects have led to six INDs,  
2           five clinical trials, and three development  
3           partnerships. Our approved projects span 20  
4           different diseases, and these diseases fall  
5           within the program priorities of 11 of the NIH  
6           ICs.

7                       There's been a very concerted  
8           effort in program outreach, and the success of  
9           those efforts is evidenced by the growth in  
10          program activity. The number of applications  
11          has nearly doubled over the last two years  
12          with 56 applications anticipated for 2010. In  
13          fact, our final receipt date for 2010 is  
14          tomorrow.

15                      The program has a bright outlook  
16          for the future. There are apparently 14  
17          projects with meritorious priority scores that  
18          are ready for our fiscal year 2011 starts, and  
19          we will be working together to figure out the  
20          best path forward to fund as many of these  
21          projects as we possibly can.

22                      Thank you.

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1                   MEMBER RUBENSTEIN: Thanks a lot,  
2                   Tom. That was informative and excellent.

3                   Let's move to Michael Kurilla,  
4                   Director of the Office of BioDefense Research  
5                   Affairs, NIAID.

6                   DR. KURILLA: Thank you.

7                   I am going to describe the NIAID  
8                   Product Development Program, the program's end  
9                   resources that we have available to advance  
10                  infectious disease product development,  
11                  specifically addressing unmet public health  
12                  needs, both in this country as well as  
13                  throughout the world.

14                  Just for some definitions, I know  
15                  everyone puts their own different spin on  
16                  these; the terminology I'll be using is you'll  
17                  see how we parse out different aspects of the  
18                  program. In terms of basic research, that's  
19                  the generation of novel scientific concepts.  
20                  It's the NIH bread and butter.

21                  What I call translational is the  
22                  exploitation of those concepts towards

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1 practical implementations of products. It is  
2 basically looking for a product.

3 And then product development is  
4 the safety and efficacy testing. It is  
5 basically looking for a licensed product as a  
6 result of those efforts.

7 I do distinguish between an early  
8 phase -- that would be IND-enabling activities  
9 into Phase II, proof-of-concept -- late phase,  
10 which would be later stage of Phase II through  
11 licensure, which are largely the domain of  
12 commercial development activities and not  
13 something we focus much on.

14 We have a multifaceted approach  
15 that basically falls into general bins,  
16 directed funding, that is, funds out to  
17 investigators, be they academic or nonprofits  
18 or biotech, and we parse those out into  
19 different bins: the basic research grant area;  
20 partnership awards, which basically covers and  
21 compartmentalizes a lot of our translational  
22 efforts; and, finally, contracts, when we're

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1 moving in later stages of product development  
2 efforts, the early product development stage.

3 And then a series of research  
4 services that comprises a wide array of  
5 repository capabilities, so that investigators  
6 are not hampered by having to reinvent the  
7 wheel, a number of specialized services that  
8 I'll describe, and then our clinical trial  
9 infrastructure capacity.

10 The direct funding mechanism with  
11 the different bins results in a series of  
12 overlapping mechanisms that allows us to  
13 basically cover the full gamut from early-  
14 stage concept generation all the way through  
15 to Phase II proof-of-concept studies. The  
16 overlap is actually desired, because that way  
17 there are no gaps that appear throughout the  
18 funding mechanism.

19 We do have a small aspect that  
20 should also not go unmatched, which is Phase  
21 IV, where we're looking. And I'll describe  
22 some of these activities that deal with types

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1 of studies that would be very desirable from a  
2 public health standpoint, but would otherwise  
3 not really be considered projects that would  
4 be incentivized for the pharmaceutical  
5 industry.

6 The partnership program, as I  
7 described, is our fundamental program around  
8 the advancing of translational activities. It  
9 specifically calls for the exploitation of  
10 basic research, trying to reduce it into  
11 usable products. This supports a wide gamut  
12 across the field in terms of vaccines,  
13 adjuvants, therapeutics, diagnostics, as well  
14 as platforms that would support the  
15 development of all of those programs.

16 The focus is exclusively on  
17 product development activities, and it  
18 requires multidisciplinary approaches. We fund  
19 them in a slightly different performance-  
20 based, milestone-driven funding.

21 And also, a clear part of the  
22 process for obtaining these awards is to have

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1 clearly-delineated product development plans  
2 that actually outline the future product  
3 development strategy beyond which our funding  
4 will, in fact, support, so that the reviewers  
5 have a notion that this product, beyond what  
6 they're asking funding for, actually has the  
7 capability to move forward on a licensure  
8 path.

9 Now, beyond the direct funding to  
10 investigators, we also lower risk for product  
11 development by providing services. We classify  
12 this under a general term of infrastructure,  
13 but it crosses the entire realm, from basic  
14 all the way through to product development.

15 There's two general categories. We  
16 have a series of specialized services, which  
17 is really activity-focused. This could include  
18 capabilities for doing sequencing,  
19 repositories, as I mentioned, which can supply  
20 a whole host of reagents for investigators, as  
21 well as screening capabilities, both in vivo  
22 and in vitro. Also, we have the capacity

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1 included in the in vivo for screening in  
2 animal models, but also for the development of  
3 specific animal models.

4 The one unique feature of  
5 infectious disease relative to a lot of other  
6 areas is that we anticipate that there will be  
7 new and unknown diseases that will continue to  
8 emerge, and that will require the development  
9 of, in fact, new capabilities for moving those  
10 forward.

11 The second aspect of our gap-  
12 filling services is a product focus, and that  
13 basically is a series of contracts that  
14 provide for us a full range of pre-clinical  
15 and clinical drug development activities that  
16 would be necessary, and we provide these to  
17 individuals, either in an academic or a  
18 biotech sector to help them advance their  
19 product forward when they run up against  
20 either gaps in their available funding or  
21 limitations in their capacity to move forward.

22 Our clinical resources -- we have

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1 a series of contracts that can provide  
2 capabilities in terms of bringing in products  
3 for testing or vaccine and treatment  
4 evaluation units. We have a Phase I clinical  
5 unit. We also provide clinical trial support  
6 services as well as clinical specimen  
7 repositories.

8 So, if you look across the entire  
9 development pipeline, we basically put  
10 together a series of various activities that  
11 can pretty much cover and allow for the  
12 capabilities to advance product development  
13 all the way forward, so that any concept  
14 should never have to be lost.

15 Now, in terms of development  
16 choke-points, as I outlined these before, you  
17 have seen that we have put a lot of effort  
18 into the development of translational programs  
19 into the early product development stage; a  
20 partnership program, pre-clinical services and  
21 clinical services, is deeply involved in  
22 moving this forward.

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1                   What we have begun to recognize is  
2                   that the translation from the basic into the  
3                   translational resources, that is, the taking  
4                   advantage or exploiting these novel scientific  
5                   concepts that we're seeing emerge, is  
6                   sometimes rate-limiting and that these  
7                   concepts can, in fact, die on the vine if they  
8                   don't get correct support.

9                   So I think this might have been  
10                  mentioned earlier this morning by Tony Fauci,  
11                  but we have put together now what we call a  
12                  Concept Acceleration Program. This is a  
13                  dedicated staff. We're assembling this staff  
14                  now. The term "sherpa teams" has been used to  
15                  describe them. They are focused on identifying  
16                  and advancing promising, novel scientific  
17                  concepts.

18                 That is a small group of people  
19                 whose effort is to identify concepts and help  
20                 investigators move through the wide array of  
21                 available services and funding mechanisms that  
22                 we have available.

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1                   It will include in their function  
2           a tech-watch type of function, which will  
3           involve other agencies, the Department of  
4           Defense, and the Biomedical Advanced Research  
5           Development Authority at HHS, so that we can  
6           pool resources in terms of everyone looking on  
7           the outside of what concepts potentially  
8           should be exploited and can be exploited.

9                   And finally, they will put  
10          together tightly-targeted solicitations that  
11          will specifically try to advance novel  
12          concepts that we feel are being generated that  
13          have further potential for development for  
14          products.

15                   Thank you.

16                   MEMBER RUBENSTEIN: Thank you,  
17          Michael. That was very informative.

18                   Our last presentation is John  
19          Gallin, Director of NIH Clinical Center.

20                   Maybe if you all start thinking  
21          about the questions and comments you would  
22          like to make, we will certainly have some time

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1           for that.

2                       So, John?

3                       DIRECTOR GALLIN: Thank you very  
4           much.

5                       What I would like to do is just  
6           familiarize with three GMP facilities at the  
7           Clinical Center.

8                       One of these you've already heard  
9           about this morning. It is the Pharmaceutical  
10          Development Service that some of you have  
11          visited. The second is about our PET program,  
12          which makes radioactive ligands, and the third  
13          is the Cell Processing Service in our  
14          Department of Transfusion Medicine, which  
15          makes cells for use in patients.

16                      So let me first tell you about the  
17          Pharmaceutical Development Section, which is  
18          in the Pharmacy Department, and it is run by  
19          George Grimes. I point out that this service  
20          has actually existed since 1956. The reason  
21          we're so excited is that just now we are  
22          opening a modern, new facility that will be

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1 fully compliant with all FDA requirements, not  
2 that we weren't compliant in the past, but we  
3 needed to upgrade.

4 So, what this service does is  
5 product development, analytical and quality  
6 control, and pharmacokinetics. It's  
7 responsible for about the 1100 investigational  
8 drugs currently under study at the Clinical  
9 Center. It formulates tablets, capsules,  
10 sterile parenterals, topical products, and  
11 including placebos, which they're particularly  
12 skilled at making.

13 It ensures that all raw materials  
14 used in finished products are suitable for  
15 human use, and it maintains accountability  
16 records for sponsor and FDA review, and it  
17 assists all investigators that NIH has needed  
18 with IND filing.

19 Their output includes in an eight-  
20 hour day about 75,000 capsules, 150,000  
21 tablets, about 220 liters of an oral  
22 suspension type of medication, preparation of

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1           5,000 syringes for administration of drugs,  
2           and 8,000 vials which can include vaccines and  
3           biologics. And that's in an eight-hour day. We  
4           could obviously increase it by running a 24-  
5           hour day.

6                       The       Department       of       Positron  
7           Emission Technology, or the PET program, which  
8           is run by Peter Herschovitch. The purpose of  
9           this program is to manufacture GMP quality  
10          radiopharmaceuticals for PET scans for  
11          patients under IRB-approved protocols.  
12          Currently, there are 21 radiopharmaceuticals  
13          available, and there's a brand-new GMP  
14          facility which is going to open up in about a  
15          year, in a couple of months.

16                      The       resources       include       three  
17          cyclotrons. This is unusual. You probably  
18          won't find this number in many places, if any.  
19          And it can include the two types shown here.

20                      There currently are 10 hot cells  
21          for synthesis of radiopharmaceuticals and a  
22          lab for pharmaceutical quality control and

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1 dispensing. There are currently three  
2 scanners, whole-body scanners, PET/CT  
3 scanners, and a High Resolution Research  
4 Tomograph.

5 And we're, I should point out,  
6 manufacturing now, we're helping to build a  
7 new PET MRI facility as part of the Traumatic  
8 Brain Injury Initiative.

9 These are the various  
10 radionuclides, the standard ones and some of  
11 the more specialized ones that are available.  
12 If you're interested, we can make that  
13 available to you. These are the 21  
14 radiopharmaceuticals that are being used and  
15 produced by this group.

16 The new PET GMP facility is going  
17 to be located in some space that was set aside  
18 in the new Clinical Center, which will be over  
19 6,000 square feet, and it will increase the  
20 number of hot cells to 19. There will be a  
21 brand-new clean room and an analytical  
22 laboratory for quality control.

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1                   This will meet all the new FDA  
2                   guidelines which are about to go into effect.  
3                   It will double our current capacity, and we  
4                   will have the capability of shipping  
5                   extramurally GMP F-18 radiopharmaceuticals  
6                   that have a two-hour half-life, if desired.

7                   The last GMP facility I want to  
8                   mention is the Cell Processing Section in our  
9                   Department of Transfusion Medicine. That's run  
10                  by David Stroncek.

11                  The mission here is to provide  
12                  cellular and gene therapy capabilities to the  
13                  investigators who would like that.

14                  The resources include a Product  
15                  Development Laboratory, a GMP Lab, and a group  
16                  that specializes in regulatory affairs. It  
17                  supports all the hematopoietic stem cell  
18                  transplant programs at the Clinical Center.

19                  And some of the IND protocols  
20                  currently in Phase I and II relate to gene  
21                  therapy, the use of dendritic cells for cancer  
22                  therapy, cytotoxic cells for cancer and

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1 lymphoma therapy, and donor leukocyte  
2 infusions.

3 In addition, there is the NIH Bone  
4 Marrow Stromal Cell Transplant Center that is  
5 supported through this program. When we are  
6 able to advance to embryonic stem cell  
7 transplantation, this group will help do the  
8 clinical aspect of that.

9 So they work 12 hours a day, five  
10 days a week right now, and they do what they  
11 call 25 intense procedures and produce 8 to 12  
12 products per week. If you ran them 24 hours a  
13 day seven days a week, we could increase their  
14 capacity.

15 I just want to end by saying that  
16 these three GMP facilities support the NIH  
17 Intramural Programs but could be expanded to  
18 assist outside investigators, if there were an  
19 interest, per the discussions this morning.

20 Thank you.

21 MEMBER RUBENSTEIN: Thank you,  
22 John.

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1                   So we would now open it for  
2                   questions for both Garret and Mary and then  
3                   the five colleagues from the NIH.

4                   Let me just begin with one, and  
5                   then we have lots of people.

6                   So, one of my questions is, with  
7                   all this wonderful work going on, why aren't  
8                   we discovering a lot of drugs?

9                   And the second question is whether  
10                  reorganization, which is I think the question  
11                  Francis is asking, of some of these programs  
12                  enhances their success.

13                  Those seem to be very relevant to  
14                  the big questions that Francis has asked us to  
15                  grapple with.

16                  Leaving aside people on the panel  
17                  could answer that, let's also ask some other  
18                  people to ask a few questions, and maybe we  
19                  can get some response from a variety of people  
20                  of the seven of you.

21                  So, Tom?

22                  MEMBER KELLY: Yes, one of my

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1 questions is related to the second issue you  
2 raised. It's pretty clear from the  
3 presentations that there is an enormous amount  
4 of capability here, and it all seems to be  
5 very high-quality.

6 It begs the obvious question as to  
7 how much coordination and interaction there  
8 are among all of you. Does RAID talk to TRND?  
9 Do they talk to NEXT? How do you relate to the  
10 Cancer Institute and the NIAID efforts in this  
11 area? Is there any NIH-wide mechanism for  
12 coordination now?

13 MEMBER RUBENSTEIN: So, why don't  
14 we get another couple of questions on the  
15 table and then the panel could respond? Who  
16 else wanted? Jeremy?

17 MEMBER BERG: So this is really for  
18 Garret, but with regard to training, you know,  
19 I guess I'm very worried about the career path  
20 issue with training a bunch of people to go  
21 into a career path that doesn't look very  
22 well-developed. One, it is likely to be

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1 challenging and, two, it may not be a very  
2 good service to them.

3 So, I know you put some ideas  
4 about the career path, and I think you hit a  
5 lot of the issues, but it seems like that is a  
6 substantial challenge that NIH can only play a  
7 limited role in helping academic medical  
8 centers figure out how to do better.

9 MEMBER RUBENSTEIN: Gene?

10 MEMBER WASHINGTON: Yes, just a  
11 related question. First, to Tom, that was my  
12 No. 1 question, too. Is there just some  
13 council or advisory group across the  
14 institutes that at least provides a forum for  
15 discussion of all the various programs and  
16 tools and technologies that are available? So,  
17 it's related.

18 But to Garret -- Garret, you made  
19 the comment that you had a preference for  
20 master's, and was that just a question of  
21 practicality in terms of the length of  
22 training that we require for Ph.D. or was

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1           there an inherent preference for master's over  
2           physician scientists, and if so, why?

3                   MEMBER RUBENSTEIN: Sure. Is that a  
4           question or an answer?

5                   Steve?

6                   MEMBER     WASHINGTON:     It's     a  
7           question.

8                   MEMBER     RUBENSTEIN:     It's     a  
9           question. Why don't we have a couple of  
10          questions? Then a variety of people can  
11          answer. Go ahead.

12                   MEMBER     KATZ:     It's,     again,     a  
13          question for Garret. That is, the concept of  
14          the CTSAs was to develop this home for  
15          clinical and translational research. You made  
16          a strong point in that direction, but how does  
17          one -- you talk about having primary  
18          appointments in this home. How does one have a  
19          primary appointment in a home that is in many  
20          parts, although heavily leveraged, in many  
21          institutions dependent on NIH funding?

22                   MEMBER     RUBENSTEIN:     All     right.

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1 Gail, you had a question?

2 MEMBER CASSELL: Well, it's again  
3 for Garret. Garret, you mentioned the  
4 importance of having an international option  
5 in terms of the training, but I wonder how you  
6 would guide NIH in terms of synergizing and  
7 capitalizing on the tremendous investments in  
8 drug discovery and drug development in China,  
9 in particular, and not missing opportunities  
10 for collaboration internationally in these  
11 efforts?

12 MEMBER RUBENSTEIN: All right. I  
13 think what we'll do is just put a few more  
14 questions on the table. Then we'll ask each of  
15 the panelists to respond. So, you'd better  
16 keep a list of all these questions.

17 Yes, go ahead.

18 MEMBER ROPER: Maybe this is what  
19 this whole conversation is about today and  
20 tomorrow, but I would welcome somebody drawing  
21 a Venn diagram to show what is the CTSA world,  
22 what is TMAT, what is Cares Acceleration

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1 Network? You know, how does this all fit  
2 together? I assume that's what you're asking  
3 advice on. I think a lot of this nomenclature,  
4 Garret, sorting out would help a lot.

5 MEMBER RUBENSTEIN: And maybe to  
6 add to that, just to add to the questions, I  
7 just wonder how many people in the extramural  
8 community know half of what's going on here.  
9 Maybe I'll say, how many of us knew all these  
10 things were going on? So maybe that kind of  
11 highlights the problem.

12 Any other questions? Yes, Dan?

13 MEMBER GOLDIN: I would like to  
14 reserve on a comment to follow up on what Norm  
15 said. So, when the questions are over, just  
16 give me two or three minutes.

17 MEMBER RUBENSTEIN: Do you think we  
18 should do that, Norm?

19 (Laughter.)

20 CHAIR AUGUSTINE: I think it's  
21 safe.

22 MEMBER RUBENSTEIN: Okay. You got

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1           it.

2                       (Laughter.)

3           Other questions or comments?

4                       (No response.)

5           So I think it was extremely  
6   informative. I mean there is an enormous  
7   amount going on. We don't know how connected  
8   it is. We don't know how visible it is  
9   outside. We don't know if it could be enhanced  
10  by collaboration or organizational change.

11                      Maybe I still come to the thing,  
12  why isn't it as effective in terms of  
13  developing new therapeutic agents as it could  
14  be and looks like it should be?

15                      So it would be really good to get  
16  some comments from our distinguished  
17  panelists.

18                      So, Garret, do you want to start?  
19  And then we'll go to Mary and down the NIH  
20  group.

21                      DR. FITZGERALD: So, as best I can  
22  remember it, I absolutely agree with you that

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1           you can't commence a training program without  
2           linking it to a careers structure. I tried to  
3           make that point, but, obviously, not  
4           efficiently enough.

5                       The worst thing in the world is to  
6           have an introductory degree program, which is  
7           why I favor the master's, just as a tool that  
8           has a broad-spectrum introduction to a very  
9           heterogenous discipline without having the  
10          coupled initiatives on the part of medical  
11          schools to actually enable the creation of a  
12          career structure.

13                     And that's why this is such a  
14          challenge, because it's a challenge to many  
15          different sectors, to funders, to academia, to  
16          industry, to regulators. And the only good  
17          thing we can say is there's a crisis for all  
18          of those camps right now, and maybe that will  
19          focus the mind on coordinative action.

20                     The reason I favor a master's as  
21          an introductory degree is because, when people  
22          begin to think about this, they come from a

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1 thousand different angles, obviously. And what  
2 you want to introduce them to is the fact that  
3 these very apparently disparate activities are  
4 actually relevant to the one that they are  
5 trying to pursue.

6 I don't favor a Ph.D. in  
7 translational meds and therapeutics. I think  
8 that would be a default mechanism for the  
9 people that didn't make it into sort of kosher  
10 Ph.D. programs as things exist at the moment.  
11 But, rather, after an introductory degree,  
12 that would be the beginning of your formal  
13 education on this process. Then you could  
14 specialize in chemical biology or  
15 bioinformatics or wherever you were going, but  
16 at least you knew that these things were  
17 interrelated.

18 And the problem at the moment is  
19 we're developing the components of the  
20 discipline as disciplines in their own right  
21 without the ability to synthesize them across  
22 those siloed barriers, as a sort of unintended

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1 consequence.

2 I think the other argument for  
3 having a sort of branding thing, which sounds  
4 trivial to an audience like this, but actually  
5 a unifying nomenclature is actually  
6 illustrated by the display of the resources on  
7 offer within the NIH. They're scattered across  
8 institutes. They are not very accessible and  
9 evident to people in the extramural community  
10 who are even interested in this.

11 And having a one-stop shop, where  
12 they are aggregated in a way that they are  
13 coordinately branded with initiatives to  
14 educate people, I think would be something to  
15 really argue for.

16 And in a sense, when we built our  
17 institute, that's what we did. We aggregated  
18 existing resources, and then we amplified  
19 them. But a lot of those resources already  
20 existed, but they were invisible as  
21 stakeholders in the process.

22 MEMBER RUBENSTEIN: Mary, did you

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1 want to respond? She left. Okay.

2 Is Jim here? Did you want to  
3 respond to any of the questions?

4 DR. DOROSHOW: I don't know if I  
5 can remember them all, but I'll try in some  
6 order.

7 So, just so that everybody  
8 understands, the NIH RAID program really began  
9 as a road map initiative that NCI sponsored.  
10 We have been intimately involved, and I think  
11 almost certainly will continue to provide  
12 toxicology and pharmacology expertise as that  
13 grows where there are overlaps.

14 I sit on the TRND Trans-NIH  
15 Oversight Board, and Dr. Austin is one of the  
16 members of our CBC Consortium. So I don't know  
17 how you would have much closer interaction. He  
18 knows everything that's going on in our  
19 program, and I have a good handle on what goes  
20 on in TRND.

21 I think the other thing that needs  
22 to be clear is that some resources are

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1           generalizable; some are not. Cancer models are  
2           cancer models. They don't help a lot for  
3           systemic sclerosis or hypertension.

4                       So, there are levels of expertise  
5           that are important with regard to the specific  
6           pre-clinical models utilized. And, also, I  
7           think it's very important -- a point I would  
8           like to make is that the linkage of whatever  
9           we do pre-clinically to having the  
10          investigators who are expert at the disease  
11          bring things to proof-of-concept, proof-of-  
12          mechanism trials. If you don't have those  
13          people who are invested in high-risk ideas,  
14          who can then, in fact, translate to patients  
15          -- there is a very small breed of those  
16          individuals who really understand enough to  
17          make a difference.

18                      I don't think, if we just only  
19          stay in the discovery space, or even if you  
20          just stay in the development space and make  
21          GMP product for people, unfortunately, in the  
22          past NCI made products for people that never

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1 got utilized because the investigator for whom  
2 we made it didn't know to file an IND. That  
3 will never happen again. We have restructured  
4 our entire program. If we make something, it's  
5 going to go into a patient.

6 But you have to have, I think, one  
7 way or another, the kinds of expertise for the  
8 disease entities that you are looking at to  
9 make things actually get from the beginning of  
10 the target to usefully be studied in a proof-  
11 of-mechanism study.

12 MEMBER RUBENSTEIN: Thank you.

13 Susan, do you want to comment?

14 DR. OLD: Yes. Yes, we all do talk  
15 a lot, TRND and CGC. So, Chris Austin is the  
16 director of those programs, and we have met,  
17 actually, with everybody at this table and  
18 half the people around this room.

19 Part of our governance structure  
20 is this trans-NIH advisory group, which every  
21 institute is invited to sit on. Some send many  
22 members; some only send one. But it is more to

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1 help us, but there is nothing to say it  
2 couldn't have a broader mission than that.

3 You asked a question about sort of  
4 an advisory council. So all of TRND's  
5 activities will go through the Advisory  
6 Council to the Director, Dr. Collins' Council.  
7 There's a working group that will look at sort  
8 of the bigger-picture programmatic issues as  
9 well as the TAG, the Trans-NIH Working Group.

10 So we do a lot of talking. We have  
11 been over to the Clinical Center. We have met  
12 with NIAID several times. We're actually very  
13 integrated with RAID. We're on NEXT. So, yes.

14 Now what I do want to say is that  
15 the people in the know are the people in the  
16 know. There are a lot of people that don't  
17 know that CTSAs exist.

18 So we go out and we give lots of  
19 talks, and we interact a lot with where we  
20 think we might get some collaboration. So that  
21 is, where do you go to find people that have  
22 these things?

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1 I can tell you one reason TRND  
2 exists is because Molecular Libraries were so  
3 successful. People were coming out with these  
4 great probes and wanting to put them in humans  
5 and not realizing there's about four years of  
6 work to take a probe to something that FDA  
7 will give you an IND for. So that's where TRND  
8 came out of.

9 But how do you do that? And we  
10 thought of a number of ways that we want TRND  
11 to help do that.

12 MEMBER RUBENSTEIN: All right. Why  
13 don't we stop you there?

14 Tom? We'll just finish up quickly.

15 DR. MILLER: Thanks.

16 I'll try to tackle the "Why  
17 haven't we made a lot more drugs?" This is a  
18 really complex question. It has a lot of  
19 answers, and I can speak mainly from the  
20 perspective of the Neurology Institute, but I  
21 think my comments are somewhat general.

22 I think these things I'm going to

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1 mention, sort of a laundry list I put down  
2 here, are things that we are working on very  
3 actively in a variety of ways throughout our  
4 ICs. So we really need to stimulate early-  
5 phase development. We need target  
6 identification and validation. We need assay  
7 development, screening assay development. We  
8 need the development and, very importantly,  
9 the appropriate use of animal models. And  
10 there's a whole area there. I could spend 15  
11 minutes on it, but I won't.

12 We have a real hole in our  
13 expertise for optimization of small molecules,  
14 medicinal chemistry in the nonprofit and small  
15 business sectors. As I say, we're approaching  
16 this from a variety -- we're trying to solve  
17 this in a number of days. It's very, very  
18 difficult.

19 We need large animal model  
20 development, which are increasingly being  
21 regarded by the extramural community and the  
22 FDA as relevant.

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1                   We need to do, and are doing, a  
2                   lot of coaching of extramural investigators.  
3                   We need to disseminate expertise and change  
4                   the mindset to applied research.

5                   So let me move quickly to, do we  
6                   talk to TRND and NCI? Oh, yes, do we ever,  
7                   very much so.

8                   So the NIH, here's the deal:  
9                   applied research, by its fundamental nature,  
10                  is interdisciplinary, and translational  
11                  research is the applied research of human  
12                  biology. When you want to combine disciplines,  
13                  you need to move to a partnering paradigm.

14                  So, what we have had in basic  
15                  science is a collaboration paradigm.  
16                  Collaboration is defined as working together.  
17                  This is what human beings don't do very well.  
18                  This is contrary to human nature.

19                  Collaborations tend to be  
20                  informal, imbalanced, to have subagendas, and  
21                  they frequently fall apart due to these, as  
22                  opposed to partnerships, which are documented;

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1           they're written down. Everybody is a winner.  
2           Everybody's role and reward is defined  
3           upfront, as is defined how the parties will  
4           part ways, if they don't get along.

5                   MEMBER RUBENSTEIN: Okay, Tom. It  
6           had better be short.

7                   DR. MILLER: This is what we're  
8           doing in NIH RAID.

9                   MEMBER RUBENSTEIN: I just want to  
10          keep it short. We've got to get Michael and  
11          John in, and then Dan has the last few  
12          minutes.

13                  DR. KURILLA: All right. I would  
14          say, to your question about why aren't we  
15          making more drugs, I think, like our  
16          counterparts in vertically-integrated  
17          pharmaceutical companies, our resources are  
18          discovering lots of promising inhibitors.  
19          Whether or not they go on to become licensed  
20          drugs that are available commercially, I'm not  
21          convinced that we're doing any less success  
22          than the large pharmaceutical companies are,

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1 and they have an overwhelming majority of "me,  
2 too" drugs which we're not focused on.

3 I think the other area that we  
4 face, which has been a struggle, and we're  
5 finding ways to address that, is that a lot of  
6 our concepts tend to be extremely high-risk,  
7 very novel, very innovative, and require some  
8 novel, innovative regulatory science in order  
9 to identify and craft successful strategies to  
10 actually develop those drugs.

11 The other component that is  
12 difficult at times is we're not going to do in  
13 general, although we can do it, if we had to  
14 do it, the commercial development activity,  
15 which means we have to transition our programs  
16 to a for-profit sector that's going to carry  
17 it forward. And in many instances, we can have  
18 products come to a Phase II proof-of-concept  
19 and not have an adequate transition partner  
20 who will take it on. The biotech entity that  
21 we have supported that has taken it that far  
22 simply doesn't have the resources and

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1 capabilities to carry that out. They need to  
2 be able to partner. And with the ever-  
3 shrinking number of large pharmaceutical,  
4 vertically-integrated companies who have the  
5 capacity, it becomes a smaller and smaller  
6 pool from which to draw.

7 So, those are the two major issues  
8 I think that are unique to a lot of the  
9 programs at NIH.

10 MEMBER RUBENSTEIN: Thank you. That  
11 was very helpful.

12 John?

13 DIRECTOR GALLIN: Yes, I will  
14 address the first question, who speaks to  
15 whom? We have spoken, as you have heard, to  
16 TRND, but we have more than spoken with them.  
17 As a result of the discussions with Chris  
18 Austin, we actually have TRND supporting some  
19 of the bench-to-bedside award programs between  
20 intramural and extramural investigators  
21 initiated through the Clinical Center. And  
22 that's this year, and it's been, I think,

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1           terrific.

2                       The second group we talk to a lot  
3           are the CTSAs. A lot of the people in the  
4           Clinical Center sit on the different  
5           committees of the CTSAs, and I participate on  
6           the PI Committee. I'm a little overwhelmed  
7           with the number of committees, but there's  
8           been good communication.

9                       Then, of course, people in the  
10          intramural programs speak to each other. The  
11          Clinical Center meets with each institute  
12          leadership once a year to plan what they are  
13          doing, and it works, but it is siloed pretty  
14          much, the planning at the institute level.

15                      I'm still not convinced that we  
16          are as good as we should be in terms of  
17          planning across the activities among the  
18          different Institutes. It's something to work  
19          on.

20                      MEMBER RUBENSTEIN: Thanks.

21                      And finally, Dan, you have got  
22          three minutes from the box here and Norm.

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1                   MEMBER GOLDIN: I will follow up on  
2                   what Norm said. He had talked about wind  
3                   tunnels at NASA. Right after the defense  
4                   industry and the aerospace industry went  
5                   through a similar situation that I see with  
6                   the pharmaceuticals, there was something  
7                   called the Last Supper that Bill Perry held,  
8                   when the peace dividend was to be paid for the  
9                   defense budget, and there was a tremendous  
10                  consolidation within the industry, and a lot  
11                  of collaboration and sharing had to take  
12                  place.

13                 The initial NASA reaction to use  
14                 the facilities: well, let's make up a lot of  
15                 money from the contractors from these  
16                 facilities and let's let the legal department  
17                 control what was going on, and let the  
18                 Congress tell us about how we ought to make  
19                 money from the contractors. It didn't work.

20                 But when the NASA leadership took  
21                 charge of it, and we recognized that we were  
22                 there, the taxpayers spent billions of dollars

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1 for the agency to put up facilities, develop  
2 technologies, develop analytical tools. All  
3 the same things I'm hearing here.

4 And we had a realistic policy that  
5 straightened out the IP ownership that didn't  
6 charge ridiculous rates, that incentivized the  
7 NASA team to say: it's not just what you're  
8 doing; you're here to support the commercial  
9 industry.

10 So there are a whole variety of  
11 facilities that got used. Overhead from the  
12 industry went down. There was a real benefit  
13 to be achieved.

14 And I really think I'm hearing the  
15 same thing now that I heard in 1992 and '93 as  
16 we went through that transition. I encourage  
17 you, Francis, to stick with it because you  
18 have a great opportunity to help the entire  
19 pharmaceutical industry of this country.

20 MEMBER BRODY: It's a great idea,  
21 except we now live in this crazy conflict-of-  
22 interest world which says this is a bad thing

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1 to do. I agree with you completely, but we  
2 have to figure out how to change the external  
3 public perception.

4 MEMBER GOLDIN: Well, what you need  
5 to do is you take a firm stand and you work  
6 with the Congress quietly, not at hearings. It  
7 takes lots of work with them, and then you  
8 work with the White House. It is workable.

9 And we worked with a White House  
10 of one party and a House and Senate of another  
11 party with incredible -- if you remember back  
12 to '94 and '95, it wasn't any easier than it  
13 is now, and you can work these things. That's  
14 my contention.

15 Now, you're not going to get 100  
16 percent, but if you settle for 30-40 percent,  
17 you've made a step forward. That's my comment.

18 CHAIR AUGUSTINE: With that, I  
19 think what we will do is cut the break down.  
20 So, we will start the panel promptly at 3:10.  
21 That's 10 minutes from now.

22 Thank you all.

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1 (Whereupon, the foregoing matter  
2 went off the record at 3:02 p.m. and went back  
3 on the record at 3:11 p.m.)

4 CHAIR AUGUSTINE: Okay. Before we  
5 launch into the next session, Francis has  
6 volunteered to present a chart to kind of  
7 offer an overview, an integrated overview, of  
8 some of what we have just heard.

9 Francis?

10 DIRECTOR COLLINS: So this is  
11 actually a diagram that you may remember  
12 seeing before. But given the questions about,  
13 "Wait a minute. How do all these various  
14 components fit together?", I thought it might  
15 be useful just for a quick context reminder to  
16 put this up again.

17 Again, this is a rather  
18 schematized and oversimplified diagram of the  
19 process of going from target identification to  
20 an FDA-approved compound with the various  
21 steps outlined there.

22 The NCGC is one component of the

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1 NIH Molecular Library. So, when you heard  
2 about that from Susan Old, that is one of the  
3 four centers funded by the Common Fund that  
4 provides expertise in assay development, high  
5 throughput screening, and medicinal chemistry  
6 to go from probe to lead.

7 The TRND and the RAID programs sit  
8 in this space of pre-clinical to try to move  
9 you, then, from a promising compound to  
10 something that could be sent to the FDA as an  
11 IND.

12 And in regard to these Phase 0, I,  
13 II, and III clinical trials, there are various  
14 players here, including, of course, pharma and  
15 biotech, the Clinical Center, and the CTSAs.

16 The new NIH/FDA partnerships that  
17 we have developed in terms of the Leadership  
18 Council with Peggy Hamburg and the regulatory  
19 science effort fits here.

20 The Cures Acceleration Network,  
21 the legislation is written pretty broadly to  
22 cover a lot of this activity, but I think the

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1 main focus is intended, again, to be in this  
2 pre-clinical space, which is often where the  
3 greatest challenges lie.

4 But this doesn't include anywhere  
5 near all of the components that are going on,  
6 and you have heard about many of them in the  
7 last couple of hours. These are basically the  
8 ones that are more centralized. Individual  
9 institutes, as you have heard, have vigorous  
10 programs of their own in translation, many of  
11 them having been derived a substantially  
12 longer time ago than any of the things you see  
13 here. And that is something that we should, I  
14 think, be glad about because this is an  
15 opportunity to do comparisons in terms of the  
16 effectiveness of various approaches.

17 The challenge, though, I think is  
18 that, while NCI and NIAID and NINDS and NIMH  
19 may have these kinds of translational programs  
20 that can actually take a rare disease or even  
21 an untouched target for a common disease and  
22 push it forward, many of the other 27

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1 institutes and centers do not have that  
2 capability. And hence, the need for some kind  
3 of centralized ability to offer those  
4 services. I think that is what this has  
5 started to do.

6 And I will say that, even for  
7 those institutes that have had active  
8 involvement in this area, when you look and  
9 see the utilization of those efforts, it is  
10 clear that there is a greater need perhaps  
11 than was being met. You saw the diagram from  
12 NCGC of where their projects come from, and a  
13 lot of them, in fact, are infectious disease  
14 and cancer, just because that's where there's  
15 a lot of opportunities now.

16 I guess from my perspective, to  
17 sort of again call back to mind the question  
18 that we're asking the TMAAT Working Group to  
19 consider here, is there an opportunity to try  
20 to coordinate this effort more effectively?  
21 The need for some kind of central approach to  
22 this does come to mind in terms of economy-of-

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1 scale issues, and that ought to be something  
2 to think about.

3 I think it also comes to mind in  
4 terms of the opportunity to do process  
5 engineering of the actual pipeline, which you  
6 could imagine doing in a circumstance where  
7 that is part of the enterprise, as opposed to  
8 a number of disconnected enterprises that  
9 don't really take full advantage of the  
10 learning process that you might get by looking  
11 at the whole landscape together. So, that's  
12 another issue.

13 I guess another thing to think  
14 about is how training can feed into this and  
15 whether that also is being optimally met right  
16 now. I think the questions that were raised  
17 with regard to Garret's presentation are  
18 highly relevant.

19 And then the whole issue of  
20 project managers and the right mechanism for  
21 actually pushing projects forward to success,  
22 which may not always fit very well with the

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1 traditional academic model of give somebody a  
2 grant and hope it all turns out well. And  
3 there again, I think one of the things that we  
4 are hoping to do with the Cures Acceleration  
5 Network encouragement is to pilot at least the  
6 effort of having more vigorously involved and  
7 empowered project managers, in addition to  
8 lots of academic investigators who are part of  
9 that team.

10 So, I don't think that really  
11 fills in all the answers to the questions that  
12 were raised a little bit ago, but maybe you  
13 get a little bit of sense of what's here.

14 There was a question raised at the  
15 break about, how many of these programs are  
16 big and how many are small? And we can get you  
17 that information.

18 One of my big concerns is that we  
19 have impedance mismatches here, that you have  
20 resources, but they are not really balanced in  
21 the way that you would like for what the needs  
22 are going to be. And would it actually be more

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1 effective to do this if that was part of your  
2 plan and you weren't just hoping that the  
3 handoff worked in terms of the throughputs  
4 that were possible in each one of these steps?

5 So, I would just stop there, but I  
6 thought it might be useful before we go on.

7 CHAIR AUGUSTINE: I think it was.  
8 Francis, thank you.

9 Okay, let's turn to our final  
10 panel of the day. And once again, these folks  
11 have kind of turned their lives upside-down to  
12 be here. So I certainly want to thank you all  
13 for your participation.

14 Our two moderators are Griff and  
15 Bill. Griff, I understand you are to start.

16 MEMBER RODGERS: Sure. So thanks,  
17 Norm.

18 I am very pleased to co-moderate  
19 this part of the discussion on bridging the  
20 gaps and defining the understanding of the  
21 necessary NIH capabilities and infrastructure.

22 I think before the break we had a

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1 fairly rich discussion of some of the  
2 infrastructure capabilities that exist  
3 certainly within our intramural program. We  
4 have heard about RAID, and we have heard about  
5 the TRND program and others.

6 Also, we heard from two  
7 outstanding colleagues on the extramural side  
8 on their concept of TMAP and how this might  
9 integrate with the CTAs.

10 We now have a group of five  
11 panelists, three from the extramural side and  
12 two from intramural, who will continue this  
13 discussion and really serve as discussants to  
14 kind of advise us on how can this  
15 infrastructure capability best be utilized in  
16 this outline that Francis just quickly  
17 reviewed for us.

18 There are several discussion  
19 questions that were provided to the  
20 discussants moving forward. So, perhaps we can  
21 start off by just having them give a brief  
22 comment related to the first discussion

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1 question, that is, what lessons are learned  
2 from the academic drug discovery that can be  
3 extrapolated to the NIH agency moving forward?

4 One of the important things about  
5 getting advice sort of in strategic planning,  
6 and obviously, it's not only what it is that  
7 you should do, but maybe also hearing what  
8 areas you should stay away from, that it may  
9 not be a profitable use of our time and  
10 effort, given what's going on in the outside,  
11 to really tackle.

12 So let me turn, first, to Dr.  
13 Bergan and ask him for his comments, and then  
14 I'll turn it back over to Bill to sort of  
15 field the questions.

16 So, Dr. Bergan?

17 DR. BERGAN: Yes, just comments on  
18 the first question. I don't have any great  
19 insights to that, but I would just like to  
20 point out that a lot of the confusion and  
21 misunderstanding that we are seeing with just  
22 the understanding of what is going on in the

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1 NIH Intramural Program with all the vast  
2 resources that are available, actually, to  
3 some extent, emulates what we have seen happen  
4 in the large pharmaceutical companies. So, a  
5 major problem still relates to integration of  
6 these large and potentially very powerful  
7 resources. That needs to be altered to  
8 increase efficiency.

9 MEMBER ROPER: I was just -- over  
10 to you -- asking the question, should we go to  
11 the others or maybe I can add a comment?

12 I think that the questions posed  
13 here are interesting, but they really all  
14 devolve to what Harold and Francis and Tony  
15 earlier said. And that is, what should NIH do?

16 We can all agree the world would  
17 work better if the world worked better, but  
18 what are the things that NIH should do in  
19 practical terms tomorrow?

20 Rob, do you want to take that?

21 DR. BERGAN: Oh, actually, that was  
22 the question I was prepared to answer.

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1 (Laughter.)

2 MEMBER ROPER: All right, go ahead.

3 MEMBER RODGERS: That is basically,  
4 what is it that we can optimally do and what  
5 probably should we not do?

6 DR. BERGAN: Yes, I think there's  
7 two broad themes that you can do. I think that  
8 the first is increase the perceived value and  
9 appreciation for someone who does research  
10 that crosses disciplines. Put whatever name  
11 you want on it, translational research, cross-  
12 disciplinary research. There is just a  
13 disincentive for people to do that.

14 And I would like to highlight a  
15 little anecdote. I also run a basic research  
16 lab. So I like to read general monographs on  
17 how to run a lab.

18 And there's one that came out of a  
19 very prominent Howard Hughes investigator,  
20 dealt with all the aspects of running the lab.  
21 This was geared to a junior investigator, but  
22 there's still some very important aspects to

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1           it.

2                       But there's one component that  
3       related to counseling a colleague who you were  
4       mentoring who wasn't doing so well  
5       scientifically, and here we're talking about  
6       basic science. And basically, the  
7       recommendation was to tell him to go into  
8       translational research.

9                       (Laughter.)

10                      And that perception actually  
11       pervades all of academia, where people who do  
12       that are perceived of lower class, not worthy.  
13       So there's a disincentive to go into that.

14                      So, I think that one of the things  
15       that NIH needs to do is to highlight the  
16       importance of these individuals, and this has  
17       been mentioned a number of times today.

18                      I think the second broad theme  
19       that NIH can do is increase the freedom and  
20       the resources given to individuals. And here  
21       I'm speaking mostly from the academic  
22       standpoint, to be able to accomplish two

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1 goals.

2 One I mentioned at the microphone,  
3 is to re-engineer the process, to investigate  
4 the specific components of the process.  
5 Because, frankly, everything that we have seen  
6 here today and everything we see with the  
7 drugs, it is all anecdotally, anecdotally  
8 failures. Even when we get the information,  
9 they're anecdotal. And anecdotal successes,  
10 and the successes are "Gosh, gee whiz." And so  
11 it's "gosh, gee whiz science." And that's bad  
12 science.

13 So there are very few things that  
14 have actually been investigated that have been  
15 hypothesis-driven. Can we get a chemist and a  
16 biologist to sit down in the same room and to  
17 actually work together to design a study to  
18 use chemi-informatics to identify new  
19 biological targets? It happens very rarely,  
20 but it doesn't in the context of a large,  
21 prospectively designed program.

22 And then the second aspect to

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1           that, which again relates to freedom and  
2           resources, is the theme of guidance. And we  
3           have all seen these diagrams going from bench  
4           into clinic and with all these points, and  
5           there's very few people who actually  
6           understand those points, all those points.

7                       I do, as a physician scientist,  
8           and I would bet most of the people in this  
9           room do, but outside of this room very few  
10          people do. And even though NIH may offer the  
11          resources, they are completely clueless.  
12          They're completely lost. They don't know how  
13          to go from step 1 to step 2.

14                     And as something to think about, I  
15          run a Phase I and Phase II chemo-prevention  
16          program out of DCP. What they did was actually  
17          really smart.

18                     How it used to work, and these are  
19          all biomarker-driven trials. So, first-time  
20          agents in demand or Phase II agents, and you  
21          are looking at cell and molecular endpoints.  
22          So, it is a nice link between therapeutics and

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1 the bench.

2 But these trials are really,  
3 really hard to run, and there's multiple  
4 pitfalls. So, what they did is they actually  
5 farmed it out to six individuals that have  
6 established track records, and they basically  
7 semi-turfed their work to individuals like me,  
8 but I deal with a smaller pool of individuals.  
9 So, they'll come to me and I help them move  
10 across the different barriers to doing this.  
11 It serves as a guidepost.

12 So, the single word I want to  
13 leave with is one thing you should think about  
14 is funding people or programs that can be out  
15 there and serve as guideposts for multiple  
16 other individuals to move across the program.

17 MEMBER ROPER: Thanks.

18 Rob, if we can just pose the same  
19 question, what could, should NIH do? And I  
20 encourage all of you to be as crisp as you  
21 can, please.

22 DR. CALIFF: It was easy with the

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1 first assignment, what lessons have we learned  
2 for an academic drug discovery? I would say we  
3 have learned we're just as miserable at it as  
4 industry has been. Any industry with a 99.8  
5 percent failure rate has problems.

6 So, then, the second question is  
7 tougher, and I'll try to be brief. I listed  
8 seven things that I'll just throw out there  
9 and not say a whole lot about, because they  
10 have all been mentioned before.

11 I think the most important thing  
12 when you are in any academic environment --  
13 and I have toured most of them that are in the  
14 CTSA because of our sort of founding role --  
15 there is a real shortage of people who  
16 actually understand the logistics of this kind  
17 of applied research. It's really quite  
18 amazing, if you take the whole faculties at  
19 major institutions. You can wander around and  
20 just get lost, and people have no idea how you  
21 go from one place to another in translation.

22 So, there is a massive need to

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1 repurpose the education and training programs  
2 if there's a belief that this is a valuable  
3 societal goal.

4 The second thing is a little more  
5 mundane, but it's really important, I think.  
6 It is the orientation away from we give you  
7 money and come back five years later to a  
8 project management approach. It's something  
9 that industry learned. Re-import it back into  
10 academia. We are actually finding, and I think  
11 others are, that it works quite well. It takes  
12 a little bit of a cultural adaptation.

13 You know, my personal anecdote  
14 there, I was telling Bob Lefkowitz, as you  
15 might imagine, when we put out our pilot  
16 grants for the CTSA, the first applicant was  
17 this young investigator named Bob Lefkowitz  
18 who needed a few dollars to do some chemistry  
19 with one of his discoveries. And when we told  
20 him that he was going to be under the purview  
21 of a project manager, he was not particularly  
22 thrilled. But it has worked out quite well,

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1 and he has founded a new company based on some  
2 of that work.

3 The third -- and there are three  
4 subcategories here -- missed opportunities, I  
5 call it. That is, if we had met in the 12-step  
6 program, we have a problem.

7 The first is that right now we are  
8 operating on a shots-on-goal environment. That  
9 is, if you fail 99.8 percent of the time, it  
10 means you've got to take a lot of shots on  
11 goal to win. And I've had a hobby of trying to  
12 find people who have successfully developed  
13 more than one drug. And there aren't many of  
14 those. And if you say, how many have really  
15 personally been at the helm of successfully  
16 developing two drugs, you get into a very  
17 select group, and most of them will readily  
18 admit for them it's also shot-on-goal.

19 In other words, if you ask people  
20 to predict early on what's going to succeed  
21 and what's not, we're not good at it. I think  
22 we all have a belief that, if we can measure

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1 systems biology more effectively and get a  
2 hint as to what's going on and all the  
3 pathways that were unintended, we could get a  
4 lot better at our probabilistic assessment,  
5 but none of us know how to do that. So that's  
6 a big area we need to focus on, I think.

7 The second has been alluded to a  
8 lot, and that's the failed effort issue. The  
9 way this whole enterprise has worked,  
10 including in academia, is if you failed,  
11 rather than talking about your failure, you  
12 want to act like you never failed and move on  
13 to something else. So there's not a record  
14 from which to develop the evidence base for  
15 probabilistic assessment. That is absolutely  
16 critical, and I think industry and academia  
17 together, we've talked about it and need to  
18 fix it.

19 The third is, I think, this  
20 boundary that I heard about, early and late  
21 phase, and industry does the late phase really  
22 well, so let's don't do it. I think that's

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1           artificial    and    a    detrimental    idea.    I  
2           understand why the NIH developed that way, but  
3           I would argue it's a different time.

4                        If you look now at what I call the  
5           "double A" of Avandia and Avastin, you know,  
6           what we have is a system where people are  
7           incentivized to work through the FDA to  
8           develop a certain kind of evidence which  
9           almost never actually tells us about the  
10          comparative balance of risk and benefit in a  
11          true sense.

12                      And coming along doing a whole  
13          other set of clinical studies to figure out  
14          how you actually ought to use a product, I  
15          think is detrimental to our society. How can  
16          you get \$12 billion in profits 15 years out  
17          from Avandia and still not know whether it  
18          kills people or helps people? And now with the  
19          vast, some of the most elegant science in  
20          history, we're in exactly the same position,  
21          and the FDA is going to have to deal with  
22          that.

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1                   So, I think the artificial  
2                   boundary is incorrect. The NIH and its  
3                   academic centers and the CTSAs, I think, need  
4                   to figure out how to do clinical trials  
5                   efficiently so it costs half as much. And  
6                   rather than seeing this as a set of handoffs,  
7                   even in that sphere, we see it as a synthetic  
8                   whole that goes from drug discovery all the  
9                   way to comparative effectiveness, and pull it  
10                  together.

11                 The last four things quickly: deal  
12                 with conflict of interest. I think there was a  
13                 good discussion about that already. I think  
14                 when you talk to young people, and we're still  
15                 sort of really dancing around what's going on  
16                 out there, it's daunting for young  
17                 investigators today to think about actually  
18                 inventing something and developing it, because  
19                 the labeling that goes on and the rules are  
20                 discouraging, frankly.

21                 The big areas, I think Garret  
22                 handled well: informatics, biostatistics,

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1 systems pharmacology, and I would add  
2 engineering, systems engineering, to that. The  
3 workforce is not what it needs to be there.

4 You can't forget globalization. I  
5 don't have time to talk about it, but I think  
6 a lot of the action is not going to be in the  
7 United States, for a variety of reasons, not  
8 all of which is lower cost, a lot of which has  
9 to do with governments deciding that the  
10 artificial boundary with conflict of interest  
11 and the way it is handled in the U.S. is  
12 putting us at a cultural disadvantage that  
13 they're going to take advantage of.

14 I'm not arguing that we shouldn't  
15 have better conflict-of-interest policies. So,  
16 we've just got to work this out.

17 And then I would just add, sort of  
18 related to the artificial boundary, we  
19 shouldn't forget we're also failing in  
20 clinical research itself. That is, if you look  
21 at an average outcome trial that we're  
22 demanding now to really measure risk and

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1 benefit, \$500 million will be a reasonable  
2 cost for a pharmaceutically-run outcome  
3 clinical trial. If you took \$200 million out  
4 of every one of those and put it back into  
5 systems biology of early evaluation of  
6 therapeutics, we would be a lot smarter.

7 And anyone who knows anything  
8 about this field knows that we are wasting at  
9 least half the money that we're spending on  
10 clinical trials on useless bureaucracy that's  
11 not helping anyone.

12 That's a short list.

13 MEMBER ROPER: Thank you, sir.

14 Dr. Halak?

15 DR. HALAK: Yes. So I guess it  
16 makes sense to just briefly talk about the  
17 perspective from which I'm speaking, because  
18 it might be a little bit different than many  
19 in the room.

20 I work at a venture capital firm  
21 that invests in early-stage medical  
22 technology. And when I say early-stage, it

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1 creates a whole debate, because what Domain  
2 used to do back in 1985 was roam the campuses  
3 of academia, find an interesting concept, and  
4 carry it forward, translate it into a product.  
5 We did that with things like FUZEON from  
6 Trimeris out of Duke, which was one of the  
7 first or was the first fusion inhibitor for  
8 HIV.

9 Because of the pressures in our  
10 business, we are less able to invest in that  
11 earliest-stage technology. And those pressures  
12 are the timeframe with which our investors are  
13 demanding their money back, and the ability  
14 for us to get their money back comes much  
15 later in development.

16 So, you know, I think this topic  
17 of translating science into viable  
18 therapeutics is a timely one, because I think  
19 it's never been needed more than now, because  
20 one of the traditional sources of funding and  
21 expertise for that in some of these venture-  
22 backed companies is diminishing.

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1                   So, with that as an introduction,  
2                   to answer the question, I'll basically combine  
3                   the questions: what can NIH do, and this first  
4                   question of, what have we learned from  
5                   academic drug discovery? I'll answer what we  
6                   have learned from some of our successful  
7                   companies that have taken early-stage science  
8                   and pushed them into products.

9                   I think there are two big things I  
10                  would highlight. One is incenting and  
11                  rewarding people towards that goal. Then the  
12                  second is -- I guess it would qualify as  
13                  project management.

14                 So, on the incenting and rewarding  
15                 side, I can tell my own anecdote that speaks  
16                 to this. I was a grad student getting my Ph.D.  
17                 with no intention really to go into academic  
18                 medicine. I always wanted to be an industry  
19                 scientist. And this is about 11 or 12 years  
20                 ago, when I told one of my thesis advisors  
21                 that I was going to join a venture capital  
22                 firm, his response was, "Oh, what a waste."

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1                   And I think that's a real problem.  
2           So, what is the answer to that? I think you do  
3           need to elevate these people. Other programs,  
4           the Chinese I know do, I think they call it A  
5           Thousand Stars Program. There's  
6           Genius Awards that have been given, something  
7           to take the best and the brightest people and  
8           drive them and incent them to go into this  
9           area.

10                   Now, those awards that you have  
11           heard about in other settings are often cash  
12           awards to get people to go into that area.  
13           Then, after that, the incentive system we  
14           obviously use in our company is equity stakes.  
15           So, giving people equity stakes in the outcome  
16           of what they do.

17                   Now, I'll leave that to you to  
18           figure out with the whole conflict-of-interest  
19           issues, but that's what I think has done well  
20           in our company, is to get people focused on  
21           the goal of driving therapeutics forward.

22                   The second area in terms of

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1 project management, I think, again, requires a  
2 cultural shift, because it's really about  
3 finding people that can manage a product with  
4 the end goal in mind. And deciding to not  
5 necessarily do the experiment that the  
6 scientist, left to his own devices would want  
7 to do, but the experiment that's going to  
8 prove if it's worth taking this scientific  
9 discovery towards the clinic or this molecule  
10 towards the clinic. That's a very daunting  
11 thing to do, because often you can get a  
12 negative answer.

13 If you keep doing basic science,  
14 you will never get a negative answer. You will  
15 always just get more information.

16 Sometimes when you're taking a  
17 molecule -- we often do an experiment -- a  
18 second best to a positive is a true negative.  
19 The worst answer is just more information,  
20 that we are just doing a lot of experiments.

21 So, we will often incent people  
22 that, if you do good work and you get a clean

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1 answer, that will be part of your bonus  
2 program. If you are good and lucky, you'll get  
3 a larger bonus, right, if you're good and  
4 lucky and it actually works?

5 So, I think these are the two  
6 things from our world of small biotech  
7 companies that I think the NIH should think  
8 about. One, incenting and rewarding people  
9 and, No. 2, this concept of what I would call  
10 ruthless program management to do the critical  
11 experiment that gets from point A to point B  
12 in the most efficient manner.

13 MEMBER ROPER: Tom?

14 DR. INSEL: Well, since I'm at NIH,  
15 maybe what I'll do is give you two or three  
16 ideas about what I think we shouldn't do,  
17 because that's perhaps one of the places where  
18 we want to mitigate risk.

19 I think it would be a real mistake  
20 for us to assume that we're ever going to be  
21 anything that looks like a pharmaceutical  
22 company or that we even want to be. We have

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1           neither the culture, the expertise, nor the  
2           incentives for any of that.

3                   And pharmaceutical companies don't  
4           want to be pharmaceutical companies anymore.  
5           So, this is not something that we necessarily  
6           want to emulate.

7                   I think Francis brought up this  
8           possibility of re-engineering the system,  
9           which makes a lot of sense, to look at what  
10          works, what doesn't. We have talked a lot  
11          internally about the quick-win/fast-fail  
12          approach rather than the shots-on-goal  
13          approach that Rob just mentioned.

14                   And thinking about, how do you  
15          really drill down on issues like proof-of-  
16          concept, and how do you really determine when  
17          it's time to pull the trigger on the biology  
18          of a new target, all of those issues that we  
19          could probably do a much better job of than  
20          has been done up until now.

21                   Also, I would stress that one of  
22          the places that we don't talk enough about,

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1 when we're talking about re-engineering, is  
2 the recognition that that canonical pipeline  
3 that everybody puts up on their slides is  
4 really only one way, and it's actually not the  
5 way that most drugs ever make it through.

6 What usually happens in terms of  
7 drug discovery and drug development, at least  
8 in the area that I work in most, is  
9 repurposing. So, that is still an area that  
10 NIH can work in and do a lot of important  
11 support, if we could get the components that  
12 we don't have access to at the current time.  
13 And there are estimates of hundreds of  
14 thousands of compounds that are out there that  
15 have been shelved by pharma that might be a  
16 really interesting sort of medicine cabinet  
17 for all of us to think about using and think  
18 about how they could be used for either rare  
19 and neglected diseases or for off-target  
20 indications.

21 So, don't become a pharma would be  
22 the first thing I would say. The second is, I

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1 think we need to get out of this box that we  
2 were talking about a little bit earlier about  
3 kind of what's intramural, what's extramural?  
4 It kind of went by too quickly to see it, but  
5 some of the things we're doing currently, like  
6 the NCGC, this Molecular Libraries effort, is  
7 an intramural program which 75 percent of the  
8 research that is going on is from extramural  
9 investigators. And that's a wonderful new  
10 model which we haven't seen enough of.

11 So, this is a place, I think,  
12 where we want to make sure we don't get bound  
13 up too much in this intramural/extramural  
14 division, because if we are going to have a  
15 new organization, and if most of it is going  
16 to live intramurally, I would hate to see it  
17 restricted to intramural scientists as a way  
18 of pushing innovation.

19 The last comment is, whenever we  
20 get into these kinds of conversations, I  
21 worry. NIH is very good on process. We spend a  
22 lot of time talking about structure and how

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1 something should be organized. But, at the end  
2 of the day, it's really the science that  
3 counts.

4 So, what we need to make sure is,  
5 however this goes forward, it is driven by  
6 scientific opportunity, by understanding that  
7 there are really important questions that we  
8 are ready to answer, rather than simply  
9 chasing something because we think there's a  
10 real need and because we are getting a lot of  
11 push to do it.

12 Those things are real, but we can  
13 spend an awful lot of time and money in areas  
14 that aren't scientifically right. So I would  
15 encourage the group, too, as we think about  
16 this, to make sure we really keep an eye on  
17 where the science is, and where it's ready and  
18 where it isn't ready.

19 DR. MATTHEW: So I can start by  
20 complimenting my fellow panelists for raising  
21 very good points, because as each point was  
22 raised, I had to sort of scratch something

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1 off.

2 (Laughter.)

3 I'm left with the challenge of  
4 saying something intelligent at the end.

5 You asked what should NIH do  
6 tomorrow. I'll start by sort of acknowledging  
7 an effort that Amy has been working on for  
8 probably two months.

9 Oh, let me first say, so I came to  
10 NIH a year ago to head the Office of  
11 Translational Research at Neurologic Disorders  
12 and Stroke, and I came from industry. I bring  
13 an industry perspective to everything I do. I  
14 came from a German company. So, it was a very  
15 efficient, a very disciplined, a very goal-  
16 oriented company, and I see some differences  
17 in the government and with extramural  
18 investigators

19 (Laughter.)

20 But what I referenced was so the  
21 Office of Translational Research, I have eight  
22 programs, all run by Program Directors that

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1 are targeted translational research.

2 So, we heard sort of a summary  
3 today of sort of the high-profile projects,  
4 TRND, NEXT, RAID. So, NINDS has more than 10.  
5 So, one thing that I think NIH needs to do,  
6 and they are working on it, is to do an  
7 inventory. What are all the translational  
8 efforts that are going on across the 27  
9 Institutes, and look at where they can  
10 synergize with one another. Because, you know,  
11 I believe most of these have grown up  
12 independently within the institutes and they  
13 don't synergize very much.

14 We heard from Susan and others  
15 that sort of the senior people, the senior  
16 leadership talk a lot and keep themselves  
17 well-informed about different programs and  
18 what's going on. But I think where there's a  
19 gap is at the Program Director level. These  
20 are the people who run these programs. They  
21 hold portfolios of grants. They're extremely  
22 busy, and I think they may hear what's going

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1 on, but there's sort of no facilitation of  
2 them having the ability to work together, to  
3 work out problems together.

4 I mean, in our translational  
5 program a big component of this is  
6 constructing annual milestones for each of the  
7 projects, assessing how they're doing against  
8 these milestones. It requires expertise in  
9 pharmacology, toxicology, all kinds of things.  
10 And we're always trying to cobble it together  
11 with the expertise in-house, and we well know  
12 that across NIH there's lots and lots of  
13 expertise at the Program Director level that  
14 really should be tapped into.

15 What can be consolidated amongst  
16 all these efforts? We should look at what  
17 would benefit from consolidation, what  
18 wouldn't benefit from consolidation.

19 But, certainly, one area that just  
20 baffled me when I came here was the whole  
21 contract mechanisms of getting things done.  
22 The idea that there could be money on the

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1           table ready to be spent, but you can't spend  
2           because you can't get access to a contract --  
3           that's crazy. And I know just this year our  
4           contracts have become even more complicated.  
5           So, you know, to what extent consolidation,  
6           getting access to pharmtx, medchem, all these  
7           things through contracts, I think would help a  
8           lot of the programs.

9                       And then, ultimately, I think we  
10          need to construct an organization that -- I  
11          will go back to my six years of German  
12          training -- it has to be disciplined. It has  
13          to be focused. It has to be very proactive.

14                      And one of the challenges I've had  
15          in helping run the translational program is  
16          sort of the mindset of these extramural  
17          investigators. Even though upfront they know  
18          that U01 is a five-year program -- the  
19          ultimate target, they must have an IND at the  
20          end of the program, five years of funding, a  
21          million dollars direct costs a year, have to  
22          hit this milestone or you're discontinued --

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1           they miss milestones and they say, "Well, I  
2           didn't know that what's a milestone was."

3                       (Laughter.)

4                       So there's a lot of education.  
5           There's a lot of information that has to be  
6           passed on, and sort of a lot, actually, a lot  
7           of guidance and discipline have to be applied  
8           to these programs.

9                       MEMBER ROPER:    Thank you. Thank  
10          you all.

11                      I think we ought to turn to the  
12          Board and ask if you want to pose questions.

13                      Griff, do you want to facilitate  
14          this?

15                      MEMBER RODGERS: Sure.

16                      Harold, your hand was up?

17                      MEMBER VARMUS: Yes. I was going to  
18          make one comment a moment ago. I would like to  
19          make it and actually three, one major, a  
20          couple of small ones, just to comment on the  
21          entire exercise we are going through today.

22                      First, I am going to tell you

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1 something that I think everybody in the room  
2 knows, but it disturbs me that we are not  
3 following what we know. Translational research  
4 is not just about target identification and  
5 drug development. There's a whole list of  
6 things that should be part of a translational  
7 research repertoire: imaging, radiotherapy,  
8 diagnostic testing, biological markers for  
9 monitoring disease, immune therapy, not just  
10 antibodies as drugs, but cell therapies,  
11 vaccines. Prevention strategies I'm hearing  
12 nothing about. Devices, even gene therapy,  
13 siRNAs, delivery mechanisms for drugs.

14 And I think we have to think about  
15 a richer repertoire of translational  
16 activities and not just we have this drug  
17 company paradigm that we're talking about, and  
18 we're massaging that, and not thinking about  
19 the many other things that NIH can do to  
20 enrich what clinical medicine does with basic  
21 research to improve healthcare. That's the  
22 main thing I want to say.

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1                   Two other just brief moments. We  
2                   have mentioned conflict of interest several  
3                   times here. We need to get some clarity on  
4                   what those conflicts are, because there are a  
5                   lot of things that even people at NIH, even  
6                   people like me or Francis who are  
7                   presidentially-appointed, can do interacting  
8                   with drug companies or other kinds of  
9                   companies. We do that all the time.

10                  We have to distinguish between  
11                  what we can do as scientists and what we can  
12                  do as private entrepreneurs, working for the  
13                  government. They are two very different  
14                  things, and I think we need to be very clear  
15                  about that if we are going to give a report.

16                  The last comment I would make  
17                  picks up on a comment that Bob Califf made  
18                  about globalization. The other face of  
19                  globalization, aside from the part you  
20                  mentioned, is the interest that we all have,  
21                  especially Francis, in global health. We put  
22                  into our formula of what NIH should be doing

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1 in the translational domain things that  
2 specifically apply to poor countries, new sets  
3 of diseases, other ways of developing new  
4 diagnostics and therapeutics that are  
5 pertinent to poor countries, and maybe some IP  
6 issues as well.

7 But we have a responsibility  
8 there, and I think that if we are talking  
9 about the translational research activities at  
10 the NIH, we ought to think about our mission  
11 as developers of science that is useful  
12 globally, not just nationally.

13 MEMBER RODGERS: Gail?

14 MEMBER CASSELL: I just wanted to  
15 ask, with respect to your comments, Bill,  
16 about the contracts and access to some of  
17 those services that are provided through RAID.  
18 What are the mechanisms for evaluating the  
19 quality of the services, turnaround time? And  
20 are these contractors really responsive to  
21 iterations? If you have results come back, say  
22 in a PK study or formulation studies, how well

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1 do you think they are working?

2 DR. MATTHEW: I don't have any  
3 first-hand exposure to the contracts. People  
4 at NCI, they're apparently the contract gurus  
5 of NIH.

6 But, I mean, they work as  
7 contractors. I mean, they have very explicit  
8 this is what has to be done; this is what you  
9 do. They deliver the report.

10 I have a contract with the  
11 University of Utah for an anti-convulsive  
12 screening program, and it's very much that  
13 way. There's a contract that specifies how  
14 many compounds they have to screen and what  
15 assays, and the compounds are shipped and they  
16 deliver back.

17 But you have a more subtle nuance  
18 there of how facile are they in changing what  
19 needs to be done. Is there somebody from NCI  
20 or maybe anyone have some insight on that?

21 MEMBER FAUCI: I'm not from NCI,  
22 but I don't understand what you're talking,

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1           your problem. I don't understand what the  
2           problem is. What about the contract? I'm not  
3           criticizing. I just don't understand it. What  
4           is it about dealing with contracts that  
5           puzzles your German-based --

6                               (Laughter.)

7                       DR. MATTHEW: So I know that RAID  
8           had six projects ready to be funded. It was  
9           coming down to the last minute. They have  
10          always had to rely on going to other  
11          institutes for capacity in contracts. That  
12          fell apart, and at the last minute it was  
13          like, where can we get contract capacity? And  
14          TRND was able to --

15                      MEMBER FAUCI: So you're talking  
16          about the NIH-employed contract managers? Is  
17          that what you're talking about?

18                      MEMBER CASSELL: No, no, no, no.  
19          This would be contract toxicology,  
20          pharmacology, PK studies, turnaround time,  
21          queues, how long it takes you to get an answer  
22          whether or not you'll even be able to access

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1           them, and waiting six months to get an answer  
2           back that should take two weeks.

3                   MEMBER FAUCI: Yes, but you could  
4           terminate a contract at the discretion of the  
5           government, if they're not performing. So, if  
6           that's the issue --

7                   DR. MATTHEW: No, no, no. I wasn't  
8           raising this as an issue that the contractors  
9           weren't performing. It was that you need to  
10          have -- so these contracts get put in place.  
11          They have a certain dollar amount to them.  
12          They're tied to the specific institutes for  
13          this much pharmatox work.

14                   If you rely on another institute  
15          to help you get this pharmatox work done, and  
16          they use that capacity in the contract, well,  
17          they can't help you.

18                   And it's not easy to create new  
19          contracts. We're working on the new contracts  
20          for the Blueprint Neurotherapeutics right now,  
21          and it is a very laborious process to put a  
22          contract in place to get this work done.

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1 DR. CALIFF: I don't know if this  
2 is helpful or not. We probably do more  
3 contract work than most research institutes  
4 because we're a clinical research institute.  
5 It's a different ball game than grants, and  
6 there are a lot more rules. You just have to  
7 know the rules, and everybody on all sides has  
8 to know the rules.

9 So, since everything is tied to a  
10 deliverable, the flexibility is not there,  
11 except dealing with the rules in a way which  
12 is prescribed. So, it just takes more steps.

13 Many academic centers or segments  
14 of academic centers aren't facile on their  
15 end --

16 MEMBER BRODY: Can I suggest that,  
17 although this may be a very important problem,  
18 that it's probably at a much lower level of  
19 detail than we need to do? Let's kind of move  
20 up.

21 MEMBER RODGERS: Richard?

22 MEMBER HODES: The conversation has

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1           been interesting in many dimensions. One of  
2           them is the relative philosophies of the  
3           investigator who pursues science for the  
4           beauty of science, discovery. And the other is  
5           management of science.

6                       And I wonder if any of you,  
7           particularly from experience, have a sense of  
8           how the ultimate reconciliation of these goes.  
9           There are a number of possibilities.

10                      One is that the basic scientist is  
11           inspired to understand that he or she needs to  
12           be managed in order to achieve a goal, and  
13           there's an evolution. The other is to set  
14           aside a separate career path, hopefully, not a  
15           second-rate path, but a distinct path, to be  
16           sure, of somebody who is trained to be managed  
17           and part of a team. Or we work as we do now.

18                      Are these destined to be separate  
19           tracks? Do we need to re-educate a large  
20           portion of our discovery scientific  
21           population? I mean, who has seen successes and  
22           challenges that lead them to think that one

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1 direction or another is the path we're taking?

2 DR. HALAK: You know, I'm not sure  
3 there's a crisp answer about distinct or  
4 pushing them together. I think you ultimately  
5 end up getting down to the level of  
6 individuals.

7 I was trying to think of something  
8 that could actually be done tomorrow. Okay?  
9 So, this is a little difficult. But I would  
10 pick up the phone and call 10 entrepreneurs  
11 that have taken science forward into things  
12 that have benefitted, you know, from basic  
13 science in human health, and have them come to  
14 the NIH and talk to people, not about science,  
15 but about that process.

16 Maybe that already happens. Maybe  
17 you already have the founder of various  
18 companies talking, again, not about their  
19 scientific discovery, but the process, and  
20 inspiring people that that's an exciting  
21 career path to pursue.

22 I think when I hear you talk

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1 about, do we have a problem in our basic  
2 science, I think there is an enormous amount  
3 of pressure -- I gave my anecdote, and I think  
4 there was another anecdote -- within the  
5 scientific community that, in fact, going  
6 translational versus basic is a second-rate  
7 career decision. So I think that is a  
8 fundamental problem.

9 And I don't think there is an  
10 institute you can put in place or a center or  
11 something that will magically change that. I  
12 think it is continually reinforcing that  
13 that's not the case.

14 DR. CALIFF: I would say, you know,  
15 we are four years into the experiment of  
16 trying to do this at an institution. And I  
17 would say the natural evolution of the science  
18 is making it so it's less of a problem now  
19 than it was.

20 That is, we have no shortage of  
21 previous discovery scientists who are coming  
22 to us saying, "I've got this thing, and it

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1 needs to be translated. Can you help me do  
2 it?"

3 I think it is an important  
4 experiment, maybe within the CTSAs, if it can  
5 be measured to see which types of management  
6 systems and interfaces on average are most  
7 effective -- although I agree, in the end, in  
8 the individual case, some people culturally  
9 are just not capable of living in that  
10 environment, and they are really good at  
11 living in the discovery environment. Other  
12 people adapt to it right away.

13 And we have had a number of people  
14 that are converted. They just love it, because  
15 they hadn't thought about things. The  
16 experience of the person five years into a  
17 project who says, "I forgot about the  
18 deliverables," a lot of those people actually  
19 like it when there's a really good project  
20 manager, often with a Ph.D., who didn't want  
21 to go into the pure basic science, but likes  
22 to manage and is friendly. It can be very

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1 positive.

2 DR. BERGAN: Yes, my read on that,  
3 it's all science. So, if you want to know if  
4 viruses can induce oncogenes, that's science.  
5 If you have shown that and want to make a drug  
6 to it, and you approach a chemist to make a  
7 drug that can specifically target that, that's  
8 synthetic science and then it's molecular  
9 pharmacology. And if you want to formulate  
10 that into something that the human body can  
11 tolerate, that's called formulation. That's  
12 science. If you want to give it to people in a  
13 Phase I and Phase II trial, that's science.  
14 And if you prove it in a Phase III trial,  
15 that's science, and then it's marketing.

16 MEMBER HODES: But, in particular,  
17 what we are hearing from a number of you is  
18 that, at the level of basic science, there's  
19 little argument that one needs to manage the  
20 scientists. As you move along the spectrum as  
21 you describe it, the requirement for  
22 management of science increases. And that's

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1 really the dimension, I think, where there's a  
2 differential receptivity or effect culture-  
3 dependent upon individual investigators.

4 MEMBER RODGERS: Tony?

5 MEMBER FAUCI: Just a comment that  
6 may have a question associated with it. I  
7 think this is going to be relevant for what we  
8 are going to be talking about tomorrow also.

9 But we went through a similar  
10 experience that I will take one minute to  
11 share with you. When we went through the flu  
12 H1N1 pandemic and we didn't have vaccine ready  
13 for the peak of the infection rate, the  
14 President of the United States brought several  
15 of us down to the Situation Room, including  
16 CDC, FDA, and myself representing the NIH, and  
17 asked, "How could it be that we invest  
18 billions of dollars in the NIH, we invest  
19 billions of dollars in the CDC, hundreds of  
20 millions of dollars in the FDA, and we deal  
21 with industry, and we have this crisis, and we  
22 can't even get a vaccine?"

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1                   So, as you might imagine, that  
2                   launched a thousand ships, including a weekly  
3                   meeting that I had in the Situation Room for a  
4                   year, meeting with the people from National  
5                   Security and others.

6                   And to make a long story short, we  
7                   got a lot of groups involved, including PCAST,  
8                   when Harold was out at Memorial Sloan-  
9                   Kettering, and he co-chaired that with Eric  
10                  Lander.

11                  And we came up with a bunch of  
12                  recommendations regarding how we can develop,  
13                  they used the word "countermeasures", but it  
14                  was really for everything. So you could sort  
15                  of pull that out and say "drugs". Several of  
16                  the things that came out were five quick ones.

17                  One is, what can the government do  
18                  to get industry more incentivized to get  
19                  involved in making products that are needed  
20                  for public health that they may not want to  
21                  make? And they recommended hundreds of  
22                  millions of dollars investment in

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1 manufacturing capacity that the industry  
2 themselves didn't think it would be worth  
3 their while making those hundreds of millions  
4 of dollars investment.

5 The other was get the FDA to stop  
6 being an obstacle, but being a facilitator.  
7 And the conclusion was that they needed more  
8 investment in regulatory science. And hence,  
9 came the recommendation that Francis and Peggy  
10 Hamburg got involved with in having the NIH be  
11 closer with the FDA in bringing science to  
12 things like developing biomarkers and ways of  
13 evaluating.

14 The fourth was a somewhat  
15 controversial one of actually creating almost  
16 venture capital-like of an organization, so  
17 that you could support companies, not  
18 necessarily products, but companies that are  
19 willing to take the risk to make products that  
20 we need that aren't high-profit margin and to  
21 be able to support them.

22 And then the other one was the one

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1           that Mike Kurilla so nicely described with the  
2           Concept Acceleration Program.

3                       And then one was how to respond  
4           better to influenza. That was the fifth.

5                       But the one that involved the NIH,  
6           after consultation with industry, with venture  
7           capitalist, with academia, some of which  
8           people were even involved in these  
9           deliberations today, the one recommendation  
10          that they made for the NIH was the thing that  
11          Mike Kurilla mentioned, was the Concept  
12          Acceleration Program, to be able to make sure  
13          that concepts that come out through basic  
14          science that we do so well don't die on the  
15          vine, that they actually can get shepherded or  
16          "sherpa-ed" through by giving them the  
17          reagents, the clinical trial capability, the  
18          animal models, et cetera.

19                      The other role that the NIH was to  
20          work with the FDA, and what Francis started  
21          with Peggy Hamburg - so, just to put it into  
22          context, it was a year's worth of weekly

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1 deliberations, and the two issues that the NIH  
2 played a role in was concept acceleration and  
3 interaction with the regulatory authority.

4 I just thought you might be  
5 interested in that.

6 DR. HALAK: What was the incentive  
7 to concept accelerate? Was there an incentive  
8 structure put in place?

9 MEMBER FAUCI: Someone had it all  
10 in one grant that they had a concept that was  
11 clear to people that could be translated into  
12 a product that would be useful for the public  
13 health, that it is likely that that individual  
14 -- and I think Rob may have mentioned that or  
15 Ray -- had no clue of how you take a concept  
16 and even get an IND. How do you deal with the  
17 FDA? How do you get it into a clinical trial?  
18 How do you get reagents to go to the next  
19 step?

20 So, money would be put into the  
21 NIH to be able to have a team of people who  
22 are very experienced in that to be able to

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1 work either with the investigator him or  
2 herself, but to take that concept and put it  
3 in the hands of an organization that can  
4 actually take it from a concept to a product.

5 So, the incentive is you get a lot  
6 of help that you wouldn't get from your grant.  
7 You get reagents. You get access to clinical  
8 trial. You get to deal with the FDA for the  
9 first time by people who have done it every  
10 day. That's the incentive.

11 DR. HALAK: And how are the people  
12 that are doing that work incented, though, the  
13 people that are responsible?

14 MEMBER FAUCI: How were the NIH  
15 people that do that?

16 DR. HALAK: Yes. Okay. So it's a --

17 MEMBER FAUCI: No, these are going  
18 to be NIH people --

19 DR. HALAK: NIH people.

20 MEMBER FAUCI: -- whose job is to  
21 facilitate a concept into a product.

22 DR. HALAK: Got it. Okay.

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1 DR. BERGAN: I think one aspect of  
2 that to consider is you used the word "take",  
3 and I know you didn't have time to formulate  
4 this, but, in essence, the basic researcher  
5 would then give it up. It would go somewhere  
6 else. Well, there would be links, but it would  
7 go to some central federal agency down here,  
8 and they would be out there, and you could do  
9 that.

10 But the point that I am trying to  
11 emphasize here is that you have to build in  
12 some maintenance of intimacy, ownership, and  
13 connectedness. If not, then it's a passing-  
14 along.

15 MEMBER FAUCI: That is a very good  
16 point. And we would love to have the  
17 investigator take that journey as an important  
18 part of that. If the person did not want to  
19 get involved, but wanted to get to their next  
20 *Nature* or *Science* paper, that would be fine.  
21 But if they wanted to be part of the  
22 partnership of taking it straight through,

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1           they could do it.

2                       DR. BERGAN: I guess what I'm  
3           saying is, no, that's not fine because then  
4           you're getting this, you know, do this little  
5           bit, and the person who knows more about that  
6           biology than anyone else in the world doesn't  
7           have much incentive and, as you allude to, is  
8           trained to just think about the next paper.  
9           So, some change in incentivization has to be  
10          built into that, so that they actually want to  
11          remain involved.

12                     DR. CALIFF: I would argue this is  
13          a legitimate debate about which there are many  
14          opinions, but, to me, it's actually at the  
15          core of what I regard as a key conflict-of-  
16          interest issue. Because at many of the  
17          institutions now, the minute you go beyond a  
18          certain step for the inventor, if there's IP  
19          involved, to be involved at the level you're  
20          describing gets to be very tricky, actually.

21                     DR. BERGAN: I don't think it's  
22          tricky. You just have to declare it. Yes, I

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1           invented this. Yes, if it makes a lot of  
2           money, I, too, will make money because I filed  
3           a patent. And, yes, I'm involved in it.

4                   MEMBER RUBENSTEIN: No, it's not  
5           that simple, believe you me.

6                   (Laughter.)

7                   There are rules against, as Rob is  
8           saying, people developing these things and  
9           having an economic incentive to do the  
10          clinical trial. So it is a complicated thing  
11          which one has to deal with.

12                   MEMBER RODGERS: Gail?

13                   MEMBER CASSELL: One thing that I  
14          would like to just remind us about, and we  
15          have talked about it before in the committee,  
16          is the development of appropriate animal  
17          models for evaluation of efficacy.

18                   And NCI used to have a program in  
19          which it specifically provided training grants  
20          for training DVM Ph.D.s and development of  
21          animal models and also for discovery of  
22          naturally-occurring diseases in animals that,

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1 in fact, are very good models of human  
2 disease, both genetically-inherited as well as  
3 infectious diseases, et cetera.

4 That program was dissolved some  
5 time ago. And I think, in fact, about five  
6 years ago, the veterinary deans got together  
7 and declared a crisis in the area of  
8 laboratory animal medicine and actually, I  
9 think, brought it to everybody's attention,  
10 but it kind of died. And I still think this is  
11 a big void and just would like to bring that  
12 up again.

13 MEMBER ZOGHBI: I actually would  
14 like to amplify Gail's point. Worst yet than  
15 developing animal models is having consistent  
16 and better characterization of existing  
17 models, putting on the shelf bad models that  
18 have been used in many pre-clinical trials,  
19 and unfortunately, led to expensive and failed  
20 clinical trials.

21 You know, I can give great details  
22 about how poor the use and characterization of

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1 clinical models have been. So I think this is  
2 really an important point.

3 MEMBER CASSELL: I could just  
4 expand on that. In the area of TB drug  
5 development there are about five different  
6 animal models, and there's no consensus as to  
7 which one is best. I think you waste a lot of  
8 money, lose a lot of time because of this.

9 MEMBER RODGERS: Well, any other  
10 comments?

11 Yes, Norm?

12 CHAIR AUGUSTINE: I'm just going to  
13 kind of weigh-in at the end of this. If I were  
14 to kind of forecast the future, I am struck by  
15 the likelihood that the private sector  
16 industry is going to invest less and less  
17 effort in basic research because of the  
18 pressures of the marketplace to produce  
19 profits next quarter.

20 That being the case, I think we  
21 are heavily dependent upon our universities to  
22 conduct the research that is going to provide

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1 the new drugs and all the other things that  
2 Harold mentioned, as funded by the government.

3 I have a concern, as I listen to  
4 the discussion, that a good academic  
5 researcher comes up with a great idea, would  
6 like to write a terrific paper, have it peer-  
7 reviewed and published, and then go on to the  
8 next paper, rather than to pursue this to a  
9 product that helps the public health.

10 The reason for that, I guess, from  
11 the discussion is that one's prestige in a  
12 community depends upon the quality of the  
13 paper rather than going out and trying to make  
14 a profit with a product. But even if this  
15 researcher is of the kind that would like to  
16 go out and make a profit with a product, I've  
17 been burned a little bit at this place myself  
18 on the subject of conflicts of interest, and  
19 it's not easy. That researcher takes a fair  
20 amount of exposure.

21 And that being the case, the  
22 question comes up, well, then how do you

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1 translate basic research into products that  
2 help public health?

3 As I listen to the discussion, I  
4 was reminded, I was involved in a tiny way  
5 helping MIT set up a systems engineering  
6 program a few years ago. And you could have  
7 substituted that discussion for the one I  
8 heard today; just put systems engineering in  
9 for translational research. It has the quality  
10 that it cuts across all the departments, and  
11 every department considers it second-rate.

12 So it is very hard to get tenure.  
13 It's very hard to get your Ph.D. approved.  
14 You're viewed as second-rate if you go through  
15 this process.

16 And where I was headed here,  
17 trying to be a little bit constructive, one of  
18 the things that helped a great deal at MIT was  
19 that I think there are 10 University  
20 professors there, and about four of them had  
21 reached the point in their career they had  
22 become very interested in big problems that

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1 kind of forced them to move out of their own  
2 field and look across the board.

3 About four of these institute  
4 professors voluntarily went into the systems  
5 engineering creation department, and it gave  
6 it instant prestige among the students and  
7 some of the faculty. And maybe I just cite  
8 that as trying to offer something  
9 constructive.

10 There may be here and elsewhere  
11 some really outstanding researchers with all  
12 the credentials that have reached a point that  
13 they would like to deal with some bigger  
14 issues, and maybe there's something there.

15 DIRECTOR COLLINS: So, Norm, since  
16 you and Dan and others have sort of pointed to  
17 historical parallels, I can't resist plunging  
18 in here, too. Because there was a time where  
19 people assumed that nobody would want to be  
20 involved in the genome project because it was  
21 mindless, because it would not give you  
22 personally much credit; you would be part of a

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1 very large team effort. You were required to  
2 give all your data away, even before you  
3 published it. Who would want to be part of  
4 that? And yet, it eventually became a magnet  
5 for some of the best and brightest scientists  
6 because of its potential impact.

7 And I think we could make some of  
8 those same arguments here. I mean, why do  
9 people go into biomedical research? A whole  
10 bunch of reasons. Curiosity is a pretty good  
11 one, the chance to learn something that wasn't  
12 known before, but, also, I think particularly  
13 because it's biomedical research, a desire to  
14 try to lead to something with clinical  
15 benefit, to help somebody.

16 I think many basic scientists  
17 probably, when they're talking to their  
18 grandmothers, refer to their own hopes that  
19 maybe what they're doing might have some role  
20 in that kind of public benefit. And to provide  
21 that as a real possibility, in my experience,  
22 is generally welcomed as, "Oh, wow, I didn't

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1 know that I could actually be part of going to  
2 those next steps." "I have no idea how" is  
3 usually the second part of the conversation,  
4 but to provide that capability is actually, I  
5 think, pretty well-received.

6 Rob has talked about this as well,  
7 and it may require, then, having a project  
8 manager who can actually make sure I don't  
9 slip back into academic mode. But there again,  
10 in the genome project we learned how to do  
11 that, and it worked pretty well, once people  
12 got over being a little ruffled by being told  
13 what to do, and that their milestones had to  
14 be met or there were going to be really  
15 serious consequences.

16 And the other attribute to the  
17 other resource that NIH would have in this  
18 circumstance is the funding. There again, it  
19 may be hard to herd cats, but you can always  
20 move their food.

21 (Laughter.)

22 It has an effect.

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1 CHAIR AUGUSTINE: I like that. Not  
2 to try to one-up you, but as Vince Lombardi  
3 said, if you are not fired with enthusiasm,  
4 you will be fired with enthusiasm.

5 (Laughter.)

6 On those two philosophical notes,  
7 I think we have reached a low point.

8 (Laughter.)

9 Let me thank each of the  
10 panelists. Again, we recognize the amount of  
11 effort you went to be here. If you have  
12 thoughts as you fly home or as you go back to  
13 your facilities as to the things you wish you  
14 had said, boy, we would welcome them. So feel  
15 free to send us emails, and that applies to  
16 anybody in the room, of course.

17 Griff and Bill, thank you for your  
18 part here.

19 Oh, yes, and as Amy points out,  
20 you are very welcome to stay tomorrow, too, if  
21 you would like.

22 We turn to the public session

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1 here, where we would like comments. We have  
2 one person who has signed up. So we would ask  
3 that individual to make their remarks and hold  
4 them to five minutes.

5 It's James Jorkasky, who is with  
6 the National Alliance for Eye and Vision  
7 Research.

8 So let me welcome you. There is a  
9 microphone there. Thank you for joining us.

10 MR. JORKASKY: I guess I'm holding  
11 everybody up from going home, but I did want  
12 to make a few comments. Thank you for your  
13 attention.

14 Again, I'm James Jorkasky. I'm the  
15 Executive Director of the National Alliance  
16 for Eye and Vision Research.

17 We are a patient and advocacy  
18 organization, also known as the Friends of the  
19 National Eye Institute. I don't speak for the  
20 NEI, but I do speak about its accomplishments.

21 I definitely appreciate the  
22 opportunity to listen to the discussions

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1           today. I'm a former research scientist, and it  
2           has kind of been my chicken soup for my  
3           intellectual soul.

4                       I had an outline for my comments.  
5           What I have done is, in between sessions, kind  
6           of scribbled in points that relate to what's  
7           been already said today to make them  
8           completely relevant.

9                       Although I realize the TMAT  
10          discussions will continue, they're in their  
11          infancy and will continue tomorrow, I did want  
12          to inform you about clinical and translational  
13          initiatives in the vision space. I am  
14          commenting for three reasons.

15                      None of the panelists so far  
16          represent vision research. Although the NEI is  
17          a relatively-small institute, it has conducted  
18          a number of smart translational collaborations  
19          that have effectively expanded its research  
20          dollars.

21                      And third, NEI's translational  
22          research includes a number of what Dr.

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1 Perakslis mentioned, patient solutions, or as  
2 Dr. Varmus said most recently, richer  
3 repertoire of translational research. That is  
4 drugs, devices, combinations thereof,  
5 diagnostics, and gene therapy.

6 Now, as the TMAP proceeds, I hope  
7 it works with the NIH staff to become aware of  
8 all of these novel and effective translational  
9 collaborations being conducted by all of the  
10 ICs within the NIH.

11 Now specifically about the NEI.  
12 Just June of this year, the NEI conducted a  
13 translational research in vision meeting,  
14 which concluded its 40th anniversary  
15 celebration. And at that event, Dr. Collins  
16 provided a keynote address where he stated  
17 that the NEI has been central to advances in  
18 translational research.

19 I think one of the reasons why  
20 that has been true is, as a relatively-small  
21 institute, it has really worked in  
22 collaborative ways inside the NIH, inside the

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1 Department of Health and Human Services, with  
2 other government agencies, with private  
3 funding organizations, and internationally.  
4 Just a few examples here:

5 Inside the NIH, it's worked  
6 collaboratively with the NHLBI, and, of  
7 course, what has come out of that is the anti-  
8 VEGFs and the FDA approval of Lucentis to  
9 treat age-related macular degeneration.

10 Also within the NIH, NEI has  
11 collaborated with the NIDDK on an ongoing  
12 series of diabetic retinopathy clinical  
13 research networks, which have come up with  
14 optimal treatment for diabetic retinopathy.

15 I mention those two because each  
16 has now resulted in a comparative  
17 effectiveness study of one comparing Lucentis  
18 and Avastin called "the Comparison of AMD  
19 Treatment Trials", and on the diabetes side, a  
20 comparison of laser photocoagulation for  
21 diabetic edema, macular edema, alone, or laser  
22 photocoagulation along with Lucentis anti-

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1 VEGF.

2 And as been mentioned earlier by a  
3 couple of the folks, there is an interesting  
4 concern about incorporating comparative  
5 effectiveness into the U.S. more completely,  
6 like it is in Europe.

7 Within the Department of Health  
8 and Human Services, NEI has now held a series  
9 of endpoints meetings with the Food and Drug  
10 Administration. What's really come out of this  
11 is not only the FDA better understanding NIH  
12 NEI-funded research, but how could that  
13 potentially impact upon potentially more  
14 progressive regulatory considerations.

15 In fact, just a week from this  
16 Friday, there will be the second of an  
17 endpoints meeting on glaucoma. It's a very  
18 exciting time in glaucoma research, because  
19 researchers are truly understanding it now as  
20 a complex neurodegenerative disease.

21 NEI collaborations with other  
22 government agencies include a collaboration

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1 with the Department of Energy on an artificial  
2 retina. Essentially, folks that have been  
3 blind for 50 years are now able to see images  
4 and navigate their homes and their  
5 communities.

6 Also, and this is one that you  
7 kind of have to see it to believe it, is an  
8 NEI collaboration with NASA on a probe that  
9 measures light scattering within the eye. And  
10 if you're sort of a quart low on your alpha  
11 crystalline in your eye, then you are more  
12 likely to develop a cataract, in plain  
13 English.

14 In the private collaborations, the  
15 NEI has collaborated with the Foundation  
16 Fighting Blindness in some really earth-  
17 shattering human gene therapy trials for Leber  
18 congenital amaurosis, which is a very virulent  
19 neurodegenerative disease. Essentially,  
20 there's been very successful initial trials on  
21 that which are now being expanded to even  
22 younger children. And again, this is a disease

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1           that usually blinds children by the time they  
2           are 20 years old. The first phase is so  
3           successful, they are now adding even younger  
4           children to that to retain vision.

5                       And finally, in the international  
6           space, because of the breakthrough work that  
7           NEI has done with the human genome project on  
8           the genetic basis of eye disease, the NEI has  
9           formed an international AMD age-related  
10          macular degeneration gene consortium,  
11          essentially, sharing information with  
12          researchers around the world, such that the  
13          latest information can be used to then look at  
14          translation and to diagnostics and to  
15          therapies.

16                      In fact, a week from this  
17          Thursday, my organization is sponsoring a  
18          Capitol Hill briefing to educate staffers  
19          about NEI's work on AMD, and it's got a very  
20          international flavor to it.

21                      So, again, I just urge the TMAT in  
22          its deliberations to not only consider all of

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1 the topics today, the cross-cutting programs  
2 within the NIH, but, of course, to take a look  
3 at the kinds of collaborations that institutes  
4 have been using to move forward translational  
5 research programs, particularly where they  
6 have had to be very smart in their use of  
7 resources.

8 Thank you.

9 CHAIR AUGUSTINE: Thank you. Thank  
10 you very much for sharing your comments with  
11 us.

12 I think that brings us to the end  
13 of the agenda for today.

14 Francis, you did mighty fine work  
15 today, heavy lifting. We appreciate that, as  
16 always.

17 Amy, do you want to give any  
18 instructions? Or does anyone want to give  
19 instructions for dinner tonight?

20 EXECUTIVE SECRETARY PATTERSON: The  
21 members are eating dinner together this  
22 evening, and Lyric has the instructions on the

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1 location. I believe that's at 6:30, but  
2 everyone will be transported from here back to  
3 the hotel. Then the place for dinner is within  
4 walking distance of the hotel.

5 DR. JORGENSEN: Actually, the  
6 shuttle will take you from your hotel at 6:15  
7 to your dinner reservation.

8 CHAIR AUGUSTINE: Does anyone want  
9 to have anything additional to say? Francis,  
10 do you want to say anything else before we  
11 break?

12 DIRECTOR COLLINS: I know this has  
13 been a day that is full of an awful lot of  
14 information, and the complexity of the  
15 question that we have asked you to address  
16 through the TMAT Working Group has, no doubt,  
17 emerged full-blown, and it may be a little  
18 daunting to try to imagine exactly how to move  
19 forward.

20 But I have great confidence in the  
21 wisdom and experience of this group. I think,  
22 again, we are not asking you to drill down

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1           into the details. We won't ask you to solve  
2           our contract problems.

3                       Hopefully, you will take the sort  
4           of larger view in the context of exceptional  
5           opportunities for developing new therapeutics.  
6           How should NIH organize itself to play the  
7           most effective role? We have, as you have  
8           heard, a lot of resources already invested in  
9           various ways. How can we get the most out of  
10          this, so that we have the best chance of  
11          benefitting patients? That's what we hope you  
12          can help us with.

13                   CHAIR AUGUSTINE: Well, that is  
14          probably a good note to close on.

15                   We will begin tomorrow morning at  
16          eight o'clock. There will be, for the  
17          panelists, the members of our group, some  
18          breakfast there before that.

19                   So, thank you and have a good  
20          evening.

21                   (Whereupon, at 4:24 p.m., the  
22          above-entitled matter went off the record.)

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