NWX-OD IOD

Moderator: Francis Collins
March 28, 2017
2:00 pm CT

((Crosstalk))

Coordinator: Thank you for standing by. At this time all participants are in a listen-only for the duration of today's call. The call is being recorded. If you have any objections, you may disconnect. At this time, I will turn the meeting over to Dr. Collins. You may go ahead.

Francis Collins: Thank you very much. Good afternoon, everybody. Welcome to a very important meeting of the Advisory Committee to the Director. Many of us gathered here in the conference room at NIH, but Members of the ACD calling in from various places. Some with access to the WebEx, but some may be needing to listen to the phone and look at the PowerPoints that we sent ahead of time.

This is a public meeting. First, let me start off however, by calling the roll to find out who is available on the phone. So, let me begin: (Russ Altman).

(Russ Altman): Yes. Back from the dead.

Francis Collins: Well, that's good. Mary Sue Coleman.

Mary Sue Coleman: Yes, I'm here.

Francis Collins: Great. (Geoff Ginsberg).

(Geoff Ginsberg): I am here.

Francis Collins: (Eric Goosby).

(Eric Goosby): Present.

Francis Collins: (Linda Griffith).

(Linda Griffith): Here.

Francis Collins: Brendan Lee.

Brendan Lee: Here.

Francis Collins: (Jeff Leiden). Not yet.

(Rick Lifton).

(Rick Clifton): Good afternoon.

Francis Collins: Good afternoon. (Ian Lipkin).

(Ian Lipkin): Present.

Francis Collins: (Peter MacLeish).

(Peter MacLeish): Present.

Francis Collins: (Elba Serrano).

(Elba Serrano): Present.

Francis Collins: (Mike Welsh).

(Mike Welsh): Here.

Francis Collins: (Roy Wilson).

(Roy Wilson): I'm here.

Francis Collins: Jay Shendure.

Jay Shendure: Yes, hello.

Francis Collins: And I know, Jay, you have to get up at 4:00, unless that's changed?

Jay Shendure: Yes, probably.

Francis Collins: Okay. As long as you can stay, we appreciate it. So, the only one I didn't hear was (Geoff Leiden). Are you there, (Geoff)? Maybe he's a little delayed. Well, we have a quorum. So, we can certainly proceed.

We have two major topics to discuss. One, which I think will go fairly quickly, but it's important – the HeLa Working Group Report.

And then, we will spend the rest of our time with a very important discussion about work plans that are associated with the 21st Century Cures Act – four of them. And we're going to need to move with great efficiency here in order to be sure that the fourth of the four doesn't get squeezed at the end, because we aim to do this within a two-hour period.

The notice of this ACD telebriefing was published in the Federal Register on February 27th. This briefing is open to the public, and listen-only lines are available. And so the public has dialed in.

If, for some reason, people are having trouble finding that dial-in number, where you can also see the materials, if you just Google NIH ACD, it will take you to the appropriate Web site, and you can drill down and find the Agenda and the background material.

And the background material will go live as we hit each topic. The material for HeLa should have gone up a couple of minutes ago. And this call is being recorded and will be transcribed, so Members and Speakers, please speak clearly, and identify yourself when you make comments. Speakers, if you could identify what slide you're on, just because not everybody will be following exactly.

(Larry Tabak) has agreed to be the timekeeper so, you know, watch your p's and q's. We'll try to keep the Agenda moving along.

So, let me then go to the first item, which is the report of the HeLa Working Group. This Group first convened in September, 2013, after we made the agreement with the Lacks family on submitting and accessing HeLa Genome

whole-sequence data via the NIH database of Genotypes and Phenotypes, otherwise known as dbGaP.

This was ably led, more recently, by Co-Chairs Kathy Hudson and Clyde Yancy. With Kathy's retirement from NIH and Clyde's completion of his tenure on the ACD, I've asked Dr. Carrie Wolinetz, who is the Associate Director of the NIH Office of Science Policy, and Dr. Lisa Cooper, who's a current Member of the ACD and the HeLa Working Group, to serve as the new Co-Chairs.

The Group want to thank Kathy and Clyde for their leadership that's been vital to the ongoing success in ensuring the Lacks Family that we are honoring their privacy and preferences.

Please, therefore, join me in welcoming Lisa and Carrie in their new roles. Lisa is not able to join us today, but Carrie will report the Working Group's findings on two data access requests that have come in since we last discussed this in December.

By the way, if you haven't heard, there is a very interesting film coming on April 22nd in HBO which is about the Lacks Family, starring no less than Oprah Winfrey. So, you all might want to take note of that.

So, thank you, Carrie and Working Group Members. Let's hear the report. Carrie, can you present?

Carrie Wolinetz: Yes. Thank you, Francis. And I'm going to move through this quickly in the interest of time, since I know a lot of this is familiar to those on the ACD. I'm on Slide 2.

And just to remind everyone, as Francis mentions, with the agreement between NIH and the Lacks Family, the researchers are requested by NIH to use the HeLa Genome Data Use Agreements for use of these cells. The role of the HeLa Genome Data Access Working Group is to evaluate the requests under these data use agreements for consistency with that agreement, in fact, and reporting the findings to the ACD, which is what we're doing today.

The — moving to Slide 4 — this is just to let everyone know who the members of the Data Access Working Group Roster are and, in particular, we appreciate the representation from the Lacks Family by way of David Lacks and Veronica Spencer.

On Slide 5, you'll see the current whole genome sequence data that's been deposited in dbGaP under this agreement.

And on Slide 6, just to remind everyone of the evaluation criteria that the Working Group uses to see whether or not, in fact, these requests are consistent with the Data Access Use Agreement — in particular, whether the proposed research is focusing on health, medical or biomedical research objectives, plans to develop intellectual property, and plans to publish or present findings.

Expanding on that further on Slide 7, the Working Group, once it's reviewed the Data Access Request, will report a finding as either a consistent/inconsistent with the data use agreement; will give a conditional notification if we need additional information, or pending, if we in fact need additional information and want to re-review that.

Just quickly on Slide 8, the Summary of our current Data Access Requests, and of particular note is that bottom line – the new requests that were being reported to the ACD today.

You'll find the details of those Data Access Requests on Slide 9. The two requests — one from the University of Michigan; one from the David Gladstone Institute — these were reviewed by the Working Group.

And the recommendations of the Working Group for both of these requests are that they are consistent with the data use agreement, and so we're bringing them to the ACD for further discussion, and votes and, hopefully, a recommendation to move forward. So, hopefully that fit within the time constraints?

Francis Collins: That was very helpful. ACD Members might have questions related to the topic, so are there questions from ACD Members about these two Access Requests, of which the Working Group is recommending for approval?

Hearing none, then we need to take a vote about whether to accept the recommendations of the Working Group. Since I can't see most of you, I think we'll do this as a voice vote. So, all in favor — well, somebody should make a motion. Let's get the Parliamentary procedure right here. Can I hear a motion about these proposals?

Ian Lipkin: So, moved.

Francis Collins: And a second?

Elba Serrano: Second.

Woman 2: Second.

Francis Collins: Okay. Lots of enthusiasm for getting this started. Now, all in favor, please say Aye.

((Crosstalk)): Aye.

Francis Collins: Any opposed?

Any abstentions?

Very good. I will consider your recommendations, as I always do, and consult with the Staff before making any final decisions, but very much appreciate your attention to this important set of issues.

With that, we can now move on to the next topic, and we're ten minutes ahead. This is great. Review of IC Work Plans from the 21st Century Cures Act. Let me just sort of point out here that it is possible — although I don't have specific information — that any member who has a conflict with one of the specific Work Plans would need to state this early and refrain from conversation on that specific Work Plan.

We're going to go through all four of them. I'm not going to ask for a vote after each one. I'd rather do this as an en bloc when we get to the end, unless there are specific issues where people wish to suggest a vote on an individual project.

So, the way we usually do this, if you're in conflict with one of them, to declare that, and then refrain from discussion about that particular project.

But you're still entitled to vote when we get to the en bloc, if that's the way we do it. So, hope that made sense to everybody.

So, is there anyone who really feels that they would not be in a position to hold forth about one of – or more of – these four initiatives because of a conflict? Then it would be good to hear that now.

Hearing none, that will make it easier. Then I'm going to turn to Dr. Tabak, the Principal Deputy, who's going to introduce the topic and make it clear to you what it is that we're asking you to do, because this is a very specific responsibility that's actually directly reflected in the legislation.

(Lawrence Tabak): Right. Thank you, Francis, and good afternoon, everybody. So, at the outset, let me remind everybody that the Plans that you are going to hear this afternoon are not yet final. They remain in draft so that we can incorporate any input that you may offer to us.

And so now, I'm on Slide Number 2, and this takes from the 21st Century Cures Act language why we are doing what we are doing. So, the NIH Director is obligated to submit a Work Plan to Congress no later than 180 days after the enactment of the Act, and that is on June 11 of this year.

The Work Plan, as I just alluded to is required to have recommendations from you, the Advisory Committee, and also it is to display the money to be obligated or expended in each fiscal year — that is, from Fiscal Years 2017 through '26 for each of the NIH Innovation Projects.

Slide 3 summarizes the Cures language that the NIH Director shall seek "Recommendations from the Advisory Committee on the amount of money to

be obligated or expended in each fiscal year for each of the Innovation Projects."

Second, "The contents of the proposed Work Plan, including the Project Description and Justification;" and last, "Whether such Projects are advancing the strategic research priorities as identified in the NIH Strategic Plan."

Slide 4 displays the four programs that will be provided support via the NIH Innovation Account, and you will be hearing a great deal more about each of these in turn.

The Precision Medicine Initiative, the Brain Initiative, the Beau Biden Cancer Moonshot and Regenerative Medicine, and on your right, on Slide 4, is a display by program of the resources that will be made available over the ten-year period, and as you can see, they are added at the bottom to give you a grand total…

Francis Collins: Which is 4.8.

Lawrence Tabak: Which is $4.8 billion.

The next slide, Slide 5, shows this same data graphically by year, just to give you the sense of the variability, in terms of the amount of resources that will be allotted. And because of this, the planning has to be quite careful to ensure that we make maximum use and are maximally efficient in using the resources that we are fortunate to have year-by-year.

The budget detail that is of importance, of course, is that these funds do not count against the so-called budget caps. And that is something to keep in mind.

And then finally, the last bullet point on this slide shows you the number of resources that NIH is reauthorized for. And as you all know, this is a two-step process. There's authorization, and then, of course, there's appropriation.

Francis Collins: You might wonder — because people have looked at these graphs and tried to discern what is the nature of this up-and-down kind of trajectory. And the history here is that in order to come up with the funds for the 21st Century Cures, offsets had to be identified.

And there were more offsets in some years than others, and that accounts for the fact that, for instance, in 2023, there is a big bump for both Brain and for PMI, and you'll be hearing from those folks about how they intend to take advantage of that.

Ian Lipkin: (Larry), would you explain what you mean by not counting against budget caps?

Lawrence Tabak: Well, let me turn to (Adrienne Halle), who could do a far better job than I can explaining that.

(Adrienne Halle): So, in 2011, the budget negotiations resulted in a statute, the Budget Control Act, that sets statutory budget caps for ten years. This funding is going to be – is proposed to be – allocated to us in the Appropriations Bill, but it doesn't count against that cap. So, it's not considered within the non-defense discretionary total.

Francis Collins: So, appropriators still have to make a specific movement to allow these funds to actually get transferred to NIH, but it doesn't count against anything else

they're doing, so they have no reason not to do that transfer. That's the point of this – not counting against the caps.

Ian Lipkin: Let me just clarify this. So, when people look at the NIH budget, overall, they're not going to consider this as part of funds allocated to NIH.

(Adrienne Halle): For the treatment – for the Congressional Budget Office and OMB, for that specific legal cap, they won't count it. How they will display it in the budget is another matter entirely.

Lawrence Tabak: Okay, thanks, (Adrienne) and Francis for those explanations, and so now, I'll turn to Slide 6.

Just to remind the Members of the ACD about the framework that was used for the NIH-wide Strategic Plan, we of course engaged the ACD in a great deal of discussion about this, and you will – reading through the individual Work Plans – understand that each of these projects, in fact, do link up to different facets of the NIH-wide Strategic Plan, and I just put this up to remind you of the sort of over-arching framework.

And so with that, unless there are any additional questions, we can turn to what are the main points of this, and that is the individual presentations. And what we will do is, we will ask each Speaker to review their materials in about ten minutes. At eight minutes I will raise my hand. At nine minutes I will approach you. At ten minutes, I will tackle you. So, we will keep to ten minutes.

And then there will be ten minutes, per-program, for the ACD to ask any questions. So, the first up is Dr. Lowy, who's the Acting Director of the

National Cancer Institute, and he will be describing the Cancer Moonshot Initiative.

Douglas Lowy: Thank you, (Larry). I want to give you an update because, as you may recall, I made a presentation about the Cancer Moonshot back in June to the ACD. And my first two slides are really a review of what I presented. But before I go further, I really want to thank both Dr. Collins and Dr. Tabak for their help in putting this information together. If we could go now to Slide 2.

The overall goals of the Cancer Moonshot, as announced in January of last year, were to accelerate progress in cancer and not just in treatment, which the Precision Medicine Initiative in Oncology from 2015 was for.

But also to include prevention and screening, and a wide range of goals — from cutting-edge research to actually wider uptake of what is already considered standard of care, but may be underdisseminated — and to encourage greater cooperation and collaboration.

And this cooperation and collaboration would be both within and between academia, government and the private sector and, importantly, to enhance data sharing. I'll now go to Slide 3.

And there were 28 members on the Blue Ribbon Panel, and they came from various sectors, and importantly included advocates, representatives from the pharmaceutical industry and information technology, several face-to-face meetings to identify recommendations and, in addition, seven working groups that comprised more than 150 members.

And the working groups had different categories, met weekly for multiple weeks and to generate several recommendations. In addition, there was input online from the public, and a number of conferences, there also was input.

And the Blue Ribbon Panel goals — we're now on Slide 4 — were to identify major scientific opportunities, poised to be accelerated by additional emphasis and funding and to identify major scientific and regulatory hurdles that can be overcome with additional emphasis on funding.

And importantly, to develop about ten recommendations of opportunities that would be pursued through the Cancer Moonshot. And the full report, which was published in October of 2016 is available at the NCI Web site at (CancerGovB-R-P) (sic) for Blue Ribbon Panel.

And this summarizes for you the ten different recommendations of the Blue Ribbon Panel and, again, gives you the Web site at the bottom. We are now on Slide 5. I'm not going to go through those in detail, but instead, we'll go on to Slide 6.

And to talk about cost-cutting themes that were developed in the discussions of the Blue Ribbon Panel, and to say that they included a National network of patient biological and clinical data, cancer prevention, health disparities research, development of biomarkers, technology and pre-clinical models, data sharing, analytics and predictive computational modeling, and collaborations, as well as the establishment of public and private partnerships.

I'm now going on to Slide 7. And Slide 7 depicts for you really a subset of the figure that you saw from Dr. Tabak of the allocation for each year specifically allocated for the Moonshot, and on the right side, the actual

amount of money. And this slide is also in the text that it was submitted about the different 21st Century Cures. I'm now going on to Slide 8.

And the approach that NCI has taken is to initiate a large amount of new research in the current Fiscal Year 2017 through '18 and '19, but some grants will use multi-year funding authority to cover out-year costs.

In the additional efforts to accelerate research will be undertaken through contracts with the cancer community managed through the Frederick National Laboratory for Cancer Research. That's just a subset of the funds.

The core resources at Frederick will be estimated to be less than $10 (billion) for FY17. And this approach will enable us to provide new grant awards every year, except for 2021. And the inability to make those awards in those two years results from the sharp decrease in Moonshot funds in '20 and '21.

This slide depicts for you what is in the text of the accompanying materials, but it shows you in tabular form the amount of money in the second column that is allocated for each year, and in the third column, the estimated amount of first-year awards.

The reason there is a discrepancy between the two is that we need to account for out-year costs as well, and that's the reason that the estimated first-year awards are substantially lower than the Cures money in dollars for each of those years.

This next slide, which is Slide 10, aligns the different proposals for FY17 for the spending with the NIH Strategic Plan, and this table is in the text as well, so I'm not going to go over it in any detail.

The next slide, which is Table 11, talks about how we propose to be funding research for FY18 through FY23. That is, Years 2-through-7, which are for the Moonshot.

And we're primarily going to do this through implementation teams that have already started to work. There is one implementation team per recommendation (except) for two of the recommendations, where there are two implementation teams for each of those two. Hence, there are 12 implementation teams.

And it is NIH intramural and extramural scientists, and it includes several staff from other Institutes and Centers in addition to NCI. And we're proposing that research with another Institute or Center – that NCI would provide twice as much funding as with the other Institute or Center.

And the charge to the teams that develop and propose initiatives for FY18 and beyond that will achieve the goals of the recommendation. We seek input from the cancer research community, including organizing workshops, et cetera, and to provide oversight and coordination of the funded initiative, including organizing meetings, providing supplements, et cetera.

And then, my last slide, which is talking about the specific new awards for '18 through '23, 8 of the 10 recommendations are going to be funded initially in FY17, and the other two will be expecting to be starting to bridge those gaps starting in '18, and we can't do this alone, so we will be building collaborations with other Institutes and Centers as well as with foundations, academia and the private sector. Thank you.

Francis Collins: Well, bravo, fitting that nicely into the timetable, Doug. Much appreciated. So, I'd like to put this now for open discussion in front of the ACD.

Questions, comments, that you might want to pose to Dr. Lowy. So, open it up.

Mary Sue Coleman: So, Francis, it's Mary Sue.

Francis Collins: Yes.

Mary Sue Coleman: And you know, I know that you've probably gone through excruciating detail in figuring out how – because the funding is coming in in such a lumpy fashion – how you're going to do this multi-year.

But is it correct that even though you're getting the money in a single year and it has to be spended in that year, can you then take those funds, grant them to an institution, and then the institution can carry over money, or no? I didn't quite get that.

Francis Collins: So, it's a great question. So, when Doug is talking about multi-year funding, basically, that means when you give a five-year award, you basically obligate all five years' worth of that money in the year that you make the awards. So, that means it, basically, has been spent. And that's the way in which you then don't take on out-year commitments for that grant. You've already paid for it.

You can see how crucial that would be in this situation because, otherwise, if we did things in the usual way, and you had a budget that went from zero to flat at 300, you'd have to spend all your money in the first year, and you'd have nothing left after that.

So, this is a way to get around that. And it's something we don't do all that often, but with this particular cost curve, you'll hear the other projects doing it as well.

I will tell you that these dollars — because they came from 21st Century Cures — are officially called "No-Year Money." That is, we are allowed, unlike a regular NIH appropriation, to carry over funds from one year to the next.

But we don't think in most instances we have to, because of the ability to do multi-year funding. So, there may be a little bit of that that the PMI program is going to try to do because of that big bump in 2023, but for the most part, we have our own mechanisms.

And you know, it's always a good idea, if you have money allocated to you, not to leave it lying there for too long, if, you know, what I mean. So, we're trying to use our own approaches as much as we can to try to make sure the allocations get spent.

Mary Sue Coleman: I'm glad you can do that. I didn't quite understand the mechanism, but thank you.

Douglas Lowy: But I think the most instructive slide that I showed is Number 9, the table of the estimated first-year awards in each fiscal year. And you can see that there is, if you will, a difference between Column 2, which is the total amount for that fiscal year, and Column 3, which is the amount of first-year award.

And the difference is made up by our doing a combination of just funding for one year, and then doing out-year funding with subsequent years. And other money is we're funding really all of it upfront, the way that Dr. Collins said.

Mary Sue Coleman: Okay, thanks.

Francis Collins: Other questions?

(Geoff Ginsberg): Francis, this is (Geoff Ginsberg). Thanks.

My question may actually be relevant to the other three initiatives that are going to be presented subsequently, but I'm just wondering if there's a bucket of money allocated to policy research that is enabling for the Moonshot, as well as for training in general, the workforce that's going to be needed to do the science in the out-years as well as to carry on from the end of the Moonshot.

Francis Collins: Doug, why don't you answer for Moonshot.

Douglas Lowy: I think it's an excellent question. And what the charge was to the Blue Ribbon Panel was to focus on science. And when there was policy issues, there was a Moonshot Task Force at the level of the White House. And essentially, those issues were brought to the attention of the Task Force, and it was the responsibility of the Task Force to address them.

In terms of training, because the charge was essentially to try to accomplish ten years of research in five, it was felt that training was not directly relevant to the Blue Ribbon Panel recommendations.

And that's one of the reasons why, when I make my presentations to our Advisory Groups and elsewhere, I emphasize the critical importance of the regular appropriation in our situation for NCI, because training is absolutely critical for developing the next generation of scientists.

Francis Collins: And maybe we want to ask that same training question again with the other projects, because there may be a somewhat different view, depending on their

duration and their need for training as central part of what they're doing. It's an appropriate question, Jeff.

Other questions?

Ian Lipkin: Francis, this is a comment. Francis, Ian.

I noticed when I was reading the Brain Initiative that it looks as though there's a lot of funding for Junior Investigators. At least that's been an early success. Is this something that you're going to emphasize here as well?

Francis Collins: You want to talk about that, Doug?

Douglas Lowy: Thus far, we have not been distinguishing between the stage of investigators. But that's really an excellent point that we should be considering.

Francis Collins: And I should say, Ian, that this is a topic that we are discussing with great intensity around the table at NIH, in everything we do; not just in things that are funded through Cures. Because we do see the need to be sure that early-stage investigators have an opportunity to get engaged; doing Principal Investigator research is critical.

And not just for that first grant, but maybe when they come back for the renewal, because it wouldn't do much good to build up our new investigators if then they're left high and dry the next time they come around. So, there's a lot going on here in that space, and it applies to everything we do.

(Walter Koroshetz): This is (Walter). I'd throw in for the Brain Initiative that since it's technology development, it's key to have the young people engaged, because

the old people are not going to learn to use these new technologies. It's going to have to be the young people.

Ian Lipkin: Yes, I can't even get on the WebEx.

Francis Collins: Point taken. Got time for another question, Larry? Yes, you're the timekeeper. Any other questions for Doug?

Brendan Lee: This is Brendan.

Francis Collins: Yes?

Brendan Lee: The implementation groups; I noticed looking at it, extramural scientists are involved. Is that primarily advisory, or will these groups actually have…

Francis Collins: It got cut off.

Brendan Lee: (Unintelligible) program would do.

Francis Collins: We couldn't get your last (phrase) because it was cut off. Can you repeat it? Brendan?

Brendan Lee: Yes. Can you hear me?

Francis Collins: Now we can. Yes.

Brendan Lee: I noticed in the extramural — in the implementation groups, extramural scientists were involved, and I was wondering whether this is primarily advisory, or do they actually have programmatic oversight, much like what extramural program would have?

Douglas Lowy: They have to be advisory, because we want the people who are giving us advice to be eligible to apply for grants, and therefore, they can't be involved in the writing and the specific development of the funding announcements.

Brendan Lee: Okay, thank you.

Francis Collins: So, got another minute or two left. Any other questions? Okay. ACD seems to be satisfied. Doug, thank you very much for that presentation and all the work that went into getting this Plan together.

Let's move now to Gary Gibbons, who is going to walk us through the plan for Regenerative Medicine.

Gary Gibbons: Okay. Thank you, Francis. I represent about a dozen ICs and Centers that have coalesced, so with interest around this promising area of regenerative medicine.

And on the next slide, part of the reason for that excitement is clearly the promise of this field and discipline, where we now have the potential to repair or replace cells and tissues damaged by injury, disease or the aging process, and really restore normal structure and function and enhance the body's ability to heal.

And in many ways, this has very wide applications, so it's really appropriate for this sort of innovative funding mechanism that can bring in to bear engineers and engineering biomaterials and tissues from different disciplines, as well as promising new technologies such as gene editing or replacement to really attack a wide variety of diseases.

The chronic debilitating illnesses that cut across all of our mission areas, as well as acute injury and congenital injury as well.

And it's with that view of the wide cross-cutting diversity of opportunities and applications that, again, this central innovative fund has utility for the NIH enterprise to which it's been an attractive opportunity for a variety of Institutes and Centers with different mission areas expand the spectrum of spinal cord injury, musculoskeletal injury, autoimmune diseases, vision, various degenerative disorders of the brain, diabetes, kidney disease, et cetera.

And so, that's in part why we have had broad enthusiasm and interest across the ICs to get engaged in this process of developing this Working Plan. And it's clear that we face a number of scientific challenges that this program may help to address that can fill in certain knowledge gaps and technical hurdles that are currently extant in our NIH portfolio.

That, again, that whole promise, we're sort of pushing this over the finish line in addressing the opportunities in regenerative medicine.

In addition, another clear challenge in this space relates to the NIH's important role in sustaining public trust and oversight and accountability. And there is a concern. Some of you are aware of the New England Journal articles that have appeared in which some applications of cell-based therapies have had adverse consequences.

And in many cases, fall outside of the purview — or have been acting outside the purview — of normal regulatory oversight, and where the public has an interest in ensuring that there's care with regard to both safety and efficacy, and that this needs to be done in a prudent and controlled manner.

And so there's a great need for rigorous science in this space and for regulatory oversight. And indeed, this program may provide us with a National platform for the dialog on that.

And indeed, an element of the program written into the Act was a collaboration between NIH and FDA that may provide more insight into a regulatory pathway in this regard.

To read specifically from the Act, it sort of specifies our charge, if you will, is "For the NIH, in coordination with the FDA, to award grants and contracts for clinical research to further the field of regenerative medicine, using adult stem cells, including autologous stem cells."

And with the budgetary restriction, not to exceed a total of $30 million. And there you can see a broad outline of the funding plan that was contemplated in the Act.

And in the next slide, you can see another key provision that has fiscal implications is the notion of a matching requirement. So, the fact that the Act stipulates really a one-to-one match of both Federal dollars with the making available of non-Federal dollars on a one-to-one basis.

And so, this is an additional element of – that, hopefully, helps us squeeze more science out of a given appropriation, but also has some implications of how we fund these awards as well.

And on the next slide, hopefully, you can appreciate that this does represent some opportunities for the NIH to, in a very focused way, catalyze, in a systematic way that spans across the NIH, approaches to advancing the field of regenerative medicine.

And one in which we have a great opportunity from the outset to work with a sister agency like FDA to further clarify a pathway by which these promising translational research can find its way into clinic and patient care.

We hope to do this in the typical fashion of being consultative and inclusive in both gaining insights from domain experts and extramural community. Obviously, we've actually already started engaging and consulting with FDA and seeing how we can again be most catalytic, leveraging existing resources in an infrastructure where possible, again, to accelerate advances in this area.

The next slide just sort of outlines again in a little bit more of a timeline fashion the allocation of funds and that pattern. Most notable is this whole process is pinned on a pretty tight timeline. And our intention is, given the Fiscal Year 17 allocation, is to go out with a notice of intent to publish.

That's sort of NIH alert and heads-up that a funding opportunity announcement is forthcoming that would take on and invite in competitive supplements as a way to sort of jump start this effort in the most expeditious fashion, and one in which we hope we can execute, actually, in Fiscal Year '17 in sort of accelerated fashion.

That takes advantage of a promising science that's already been peer-reviewed by NIH but gives an opportunity for those matching funds to come, and for those projects to advance and extend their work in a compelling way.

And in the meantime, in parallel, be proceeding forward with funding word announcements to land in Fiscal '18 and beyond to invite more investigator-initiated new projects that again can be responsive to this Act and to our objectives.

And so, in that regard in the next slide, we put forward to you this Working Plan in which other criteria will follow the usual ones of merit, but clearly we're looking for the ability to supplement funding to promising immediate use to underlying projects that have already some momentum.

And would be further accelerated by these funds, and that have the promise of attracting matching funds to, again, further extend the bang for buck in ways that, again, can fulfill the objectives as outlined here.

I'll proceed to the next slide, which is the final one, which invites the input of the ACD that, again, related to the relative formative nature of Regenerative Medicine Initiative, relative to some of the others. Your thoughts about where you see potential opportunities, challenge areas of focus, or topics that are particularly right. And appreciate your input.

Francis Collins: Terrific. Thanks, Gary. Let me open it up to the ACD for discussion.

Roy Wilson: This is Roy. I've got a question.

Francis Collins: Yes, please.

Roy Wilson: And let me know if you can't hear me, and I'll hop off my treadmill. So, the matching funds — Gary, where is it contemplated that these funds would likely come from?

Gary Gibbons: Well, the main stipulation is that they're non-Federal. And so, it's…

Roy Wilson: Wouldn't that be mainly from, you know, university reserves, or I mean – I'm just asking what would be the likely source of this?

Gary Gibbons: Right. Well, as a University President, I'm sure you have access to philanthropic foundation donations that are non-Federal that could be appropriate for matching. Similarly, in many States, there are activities in this space in which State funds that don't derive from a Federal allocation could be used as matching.

And clearly, there may be organizations, nonprofits or, indeed, the private sector that might see an opportunity to contribute to this area. We're also contemplating that the matching could be in the form of in-kind, and so there could be an entity that has a resource that's critically important for the implementation of a project, and there may be other ways to do the matching.

We hope to provide guidance to really help the community understand what would qualify. Hopefully I addressed…

((Crosstalk))

Roy Wilson: I think that using this mechanism to (exempt) State Government to come up with some sort of programs to use non-Federal dollars to bring research into their States might be actually quite good.

I do hope that this phase is a limited NIH kind of venture, and that it doesn't become the norm, because I do think it would change the entire historical relationship of the NIH to universities.

Gary Gibbons: Your points are well taken. I think part of the notion here was for this investment to be catalytic and bring together partners in this space, again, to push things over the finish line, and it may need a number of different partners in addition to NIH to make it happen, so it's really in that spirit.

Roy Wilson: Thank you.

Mary Sue Coleman: I guess I'd like — this is Mary Sue — and I'd like to sort of go along a similar vein. And it's curious to me this seems to be the one area where this matching idea has emerged and, you know, clearly, it's the smallest portion of the funding. And it looks like that what you're trying to seek are things that are really ready for the bedside.

I mean, it's just curious. And I don't disagree with Roy, though I will say that, you know, for many universities who already feel like that they're matching in kind with incomplete coverages or indirect costs, this just seems odd to me. And could you explain a little bit more about the thinking? And I think you're going to get a lot of discussion about this.

Gary Gibbons: I'll take a stab, and give it to Francis here. One thing that, for my own at NHLBI, we have a fairly substantial investment already with the extramural community, in which we make investments through traditional pathways – academic institutions – so, from the NHLBI, in the tens of millions of dollars per year in this broad, regenerative medicine space.

And so I think — although I appreciate the concerns raised — that this really has a particular focus in this program of innovation, in which it is an opportunity to explore a different model that, again, hopes to bring together different stakeholders to accelerate and catalyze things that aren't already happening. So, I think it's in that perspective that this ought to be looked at.

Francis Collins: So, yeah, (Mary) your question's appropriate and this part of the cure still, as you know had a great deal of interest in the Congress because of their concern that there were great opportunities here in terms of clinical applications of

autologous stem cells that somehow were not being pursued as vigorously as they hoped they would be And I think the notion was that they would be able to go in a direction with new partnerships that could also be beneficial.

And this was a way of encouraging in a very direct financial way those kinds of partnerships. Perhaps they have noticed some of the other things we've done in terms of partnering with the private sector, like the accelerating medicines partnership. And they also could see that there were some other natural partners out there.

I think they were also hoping that some of the other sources of funding that might be going forward anyway would by this mechanism form a coalition with NIH and that that would be good for the science, because we would tend to bring to this our own sort of way of doing careful study design and review, and that that would be good for everybody.

But it is a bit of an unusual circumstance. We haven't seen this kind of mechanism proposed quite this way before and to reassure (Roy) I don't think this is the start of something that's going to suddenly spread widely throughout our whole portfolio. It's sort of an experiment in a very special place where yeah, Congress really did think of this as hurry up and see what we can do about clinical applications.

Mary Sue Coleman: Okay, that's helpful, thanks.

(Peter MacLeish): Now this is (Peter)

Francis Collins: Yes.

(Peter MacLeish): My sort of early response to this is that it is grossly underfunded. Both in terms of money and time. I mean, as I look at, what is missing is some basic science knowledge in terms of how to go from undifferentiated cells to a fully differentiated cell that you're sure about. Or to go from a fully differentiated cell back to an undifferentiated and back to differentiation.

There is tremendous, there are gaps that are just enormous and I, somehow this doesn't seem to be addressing those gaps in knowledge. I'm not sure we're ready to go to the bedside yet.

Gary Gibbons: So again a great point (Peter), one that our coalition of, sees, are wrestling with as well. I'd agree with you that's where it's important to keep in mind that there is a larger pool of investment that's happening concurrently with this innovation fund that a variety of institutes are already engaged in, and I agree with you that it will be that sort of complementary effort that'll be essential.

There's still a lot we don't know about stem cell biology that clearly needs to continue, and again I think (Francis) articulated the intent here, probably Congress that if indeed there are some things that are closer to application in the clinic, that we may be able to nudge a little over the finish line. I think that was the challenge to us, and as we explore this I think we will find that those opportunities may indeed emerge, and I think that's the intent.

Francis Collins: (Peter), your comments are very well taken. I think it's important maybe to mention that NIH is funding hundreds of grants on stem cell biology, many of them actually quite basic science in terms of trying to understand the steps involved in differentiation and de-differentiation. it's an enormously exciting area.

This is basically an additional layer of special funds coming from the Cures Act which they intended to have particularly focused on whether there are opportunities in autologous stem cell therapeutics that would not necessarily have to wait longer for a lot of the basic science to happen. And we take that encouragement and we will try to use it wisely.

But this is actually a small percentage of the overall funds that we'll be spending on stem cell research over the next four or five years.

(Peter MacLeish): (Francis), that's true for every area here, right. You're spending a lot of money in cancer, a lot of money on brain cells. These are not, these are certainly additions. I'm just struck by the proportion between what's there and NIH and what's been put into these mechanisms. Also, what about the time? This goes to 2020? Just a few years, right, the others go to 2027, did I get that right?

Francis Collins: Yeah, this is just four years.

Gary Gibbons: Yes.

Gary Gibbons: Though with some of the funding mechanisms' flexibilities that were described earlier there might be opportunities to extend that window, but again, the cap being the $30 million.

Francis Collins: We agree it's a very modest contribution, we didn't get to set the dollar figure, that's what the Congress of the United States decided to put into the bill, and again important to recognize that this is an additional increment for which we're grateful, on top of what is already a pretty significant investment by NIH.

Linda Griffith: So this is (Linda), just one comment to (Peter). there are, you know I haven't been on NIA's council as well as involved in regenerative medicine. There are a number of studies that a lot of basic science has been done, but it's really hard to fund the large animal trials that would give you that really definitive data that would let a company or someone pick it up and take it to the clinic.

So I can imagine, and I know for example investigators at Cleveland Clinic and (unintelligible) who were really poised to push something over the edge and go into the clinic-based availability of funding for large animal trials, which is really hard to get out of institutes like NIAM. So there may be some things coming out of the woodwork that are really quite close to clinical implementation that could benefit from this and could get matching funds.

Francis Collins: Great, and thanks…

Gary Gibbons: To add to that same point, I think this is an area where in collaboration with FDA we might be able to clarify what would be the pre-clinical and other enabling elements necessary for this to go all the way to patient care. And this could represent one of those opportunities. Just as you said, how much pre-clinical work that needs to be done and in safety and efficacy, so there are some opportunities for certain technology applications.

Francis Collins: The timekeeper is nudging me to say that we have hit our time limit for this particular discussion unless somebody has a very strong point they need to make. Okay, hearing none, let's move to precision medicine initiative, which is a topic that some of you who've been on the ACD for a while will know quite a bit about, having been in many ways serving a role of parents of this enterprise through the working group that (Rick Liston), who's on the phone, shared with (Kathy Hudson), which is now taking shape and which (Eric

Dishman) will tell you about, and especially link up to the funds that are provided in the 21st Century Cures Act. So (Eric).

(Eric Dishman): So it's great to be back here with you. For those of you who don't have your dog-eared copy of the ACD working group report, I do, I had to recently reprint it because it had so much, there was no space left for marginalia. We do use that as a report to really guide what we're doing. It came out in September of 2015 but is something that's quite present, at least in our lives.

You know, most of you know the program well but just as a quick overview. Unlike the programs that you've seen so far, it's a very different kind of use of resources. We're not funding awards that are about the research, but we're funding awards to build a national resource. And our goal is to accelerate scientific discovery and medical breakthroughs in precision medicines with the resource that hopefully, you know, eventually hundreds if not thousands of studies will use to amplify a wide range of scientific questions and fields.

On the right, what the essence of this program is, often what I call quadruple or I've started to call quintuple diversity, we are recruiting a diversity of people from across the country, a diversity of geographies and making sure we're covering a wide range of geographic settings, a diversity of data types, a diversity of health status, because we're not recruiting people with a particular disease. And also we want to enable a diversity of researchers.

One of the priorities is to build tools and capabilities that bring more people into the biomedical research sandbox so that it's not just, you know, the tier ones who have the ability to do genome studies. It's really, you know, citizen scientists and others on the education continuum who can do that.

And I think most of you know there's two primary mechanisms that we've built out. The direct volunteer mechanism, anybody in the country saying "I want to be part of this," here's a 1-800 number or click here. And then a network of health provider organizations who have both scientists who help guide the science of what we're wanting to make sure this is useful for, as well as recruiting people from their memberships, from everything from small, federally qualified health centers to large players, like regional centers like Geisinger and the Veterans Administration.

If you go to slide four, just a quick status, I won't go through all of these. On the right you see the major building blocks, everything from the data and research center, which is the sort of the big data central and the data repository, to the Biobank and building out that capacity to be able to reach people in parts of the country through the participant technology systems via the web or the 1-800 number.

Probably the least built out is the bottom right, the community engagement partners. We're just reviewing the first awards that came in for that and we'll be releasing those. And those are community partners, everything from churches in a particular area to large not-for-profits who can help educate and build a relationship with communities on the ground, especially where we don't have health provider organizations. leveraging that direct network of Walgreens and Quest and others, but somebody needs to be the face and the relationship and a trusted local partner to really help bring those communities into it.

What I'll tell you is, the basic status is we just got the IRB response, which we think will be the last round of the version one protocol. We're frantically working on giving a response to them within a week or two, and we're moving, all pieces are coming together from the Biobank infrastructure,

everything's being thoroughly tested and in about three weeks, we will have everything in place to where we can start to test things end-to-end for what we call a period of consortium testing

So the consortium testing is not just testing the pieces, but when everything's brought together with all of the workflows and all of the elements, making sure all that infrastructure works, and then targeting a launch of an alpha and beta phase for each of the health provider organizations in the initial direct volunteer sites in May.

Again assuming we get through final IRB approval as well as the testing results go well, and if we are able to do that in May, real people, real protocol end-to-end systems, that'll test about the first 25- to 30,000 people, and then aiming towards a national launch in the October timeframe. And what I will say to you is what I say to the team every day, and what we're trying to help everybody understand, we will launch when ready and right. We test constantly and you know, we'll make sure that things are working before we scale them up at large scale.

But the team's pretty excited, it's becoming very real very quickly. On slides five, you know, we, these are estimates that we have and this is just some of the big ticket items of, you know, with ten years of what this program costs, we've estimated $4.3 billion, this has been a consistent estimate that we used to initially sort of scope this out. And you can see some of the big ticket items, and there's big things like whole genome sequencing and werables that if we did today would be a billion for each of those over ten years. We, you know, want to ride those cost curves down as technology changes so that we can look forward to scale those things.

Just a reminder of the 21st Century Cures funding on slide six. And it reiterates many of the main themes of the ACD working group report, having a network of (unintelligible) who can use and inform this resource. Especially wanting to make sure that we get to know genomic technologies included and focusing on the diversity of the cohort. We're aiming for 75% of these million people to be those underrepresented in traditional biomedical research, and as you see our own sort of funding curve that jumps up and down and as Dr. (Collins) pointed out earlier, the largest amount of funding in 2023 with $419 million.

So what I'm going to share with you on slide seven and really the most important part of the next three slides is just an estimate of plausible scenarios of how we will use that cost over time. Unlike being able to, with some of the other presentations where we can say "Hey, we're going to do $25 million grants," you know this is infrastructure and these are technologies and these are things that we will learn how to optimize the costs of over time.

The first of these is if we had full funding, and originally we had proposed ramping this project to $430 million a year, then this is the basic element. It would put us in a cadence of releasing protocols every third year, so version one is what we're about to do, and each one of those has a biosample collection that needs to be associated with it as well as maintaining all of the previous biosamples that we already have.

Down below you'll see the Biobank capacity needs to increase, we're building out the Biobank capacity for 35 million vials, which is version one. But you know at one point as we start to scope out versions two and three we'll have to increase the Biobank capacity.

It will take us with full funding until about the end of 2020 we believe to ramp to a million people, and you see per clinical data, primarily from EHRs but not exclusively, we start with more simple things like EHR summaries and labs and we're building that capacity right now for those initial health provider organizations, and we're doing pilots of capabilities through the direct volunteer mechanism.

We're also planning to do pilots with the base funding, very soon, of genetics and then move to genotyping and whole genome sequencing. There's still a public comment period going to be set up to give input to all of that, so we don't know exactly what the genomics plan is yet. And then version one and version two and version three of the Biobank as I mentioned before are linked to that.

What changes in scenario one, which, and the big question here is, we don't know yet what our baseline budget is supposed to be. The Cures money is supposed to be additive. We're assuming that it might be to help just pay for the baseline, and in a scenario where our baseline budget never ramps to 430 but stays at 230, you can see that we can still hit most of our deadlines pretty well. We still think we'll do biosample collection on an every third year cadence. It pushes out the pilots for the genetics, it pushes out when we might build a special device for wearables. But we can get pretty darn close, it pushes things out in time with 230.

If our baseline budget gets stuck at what it is this year, which is $139 billion, then we need to use the Cures money to pay a whole lot more of the infrastructure bills, and it does push out in time with some risk, you know when can we start pulling in richer EHR data? When can we actually start to do whole genome sequencing? And you know, when are we going to be able

to create the diversity of data types which were one of the fundamental pillars of this program as we go forward in time.

So it basically kind of, you know, how I want to end this and sort of plant seeds with you is again understand that we don't yet know our baseline budget. So how we spend the Cures money will depend a lot on what ends up happening with the baseline budget. The good news is we're close to launching version one and the good news is even for that lower current budget of $130 million, we can make great progress on this program.

And you know while we all have to know that we're going to learn as we do the alpha and beta phase in the first year of the national launch, about what things really cost and we'll change and optimize those over time. But neither scenario one or two would get us to our full budget.

So it does force some tradeoff discussions, in particular for us it would be helpful to hear from you on the balance of you know, valued participants, to valued researchers. And in particular this question of, you know, if we had the lower budget, which is more important, 100 million people or the depth of the data collection we might do on a smaller number of people.

So I think, you know, that's our current situation and would welcome your comments or your input depending on how fate unfolds before us.

Francis Collins: Thanks, (Eric), let me just clarify one thing about this, two different scenarios of what the base budget is, in case that wasn't completely clear from the materials we sent you. So the current base that was in FY16 was $130 million for this project. FY17, you may know we're in a continuing resolution, which means you basically keep going with what you had the previous year. But

that continuing resolution will need to be reconsidered by April 28 because that's when it expires.

The House and the Senate appropriations committees last summer, when they were marking up the FY17 year-long bill, which never made it, at least not yet has made it into reality, were enthusiastic about this program and in their particular versions of what they thought would be appropriate, and did give this $100 million increment, which would get it up to 230.

We remain hopeful that the Congress will by April 28 revisit this question of FY17 and provide some additional support for NIH, which would include this. And so that number's not taken out of the air, but it has to be considered at the moment as hypothetical, given that the Congress has a lot of things on their plate right now. Just want to put that in context. So let me open this up to ADC for questions, discussion.

Ian Lipkin: (Francis), this is (Ian), I have a couple of questions. The first is when we first saw this presented we had a discussion about whether or not this was going to be focused exclusively on genomics, or there are going to be functional assays, exposure assay, and as I'm seeing looking at this presentation I see a very large genomics project but it's unclear to me that we're going to be able to do microbiome analysis, proteomics, metabolomics, am I missing something?

(Eric Dishman): No, you're not missing anything. It is very much the case that we will be doing those, we don't have the assay plan. Again, we're convening groups of scientists and institutes here at NIH to help inform what those will be. They're subsumed, a certain amount of them are subsumed within the cost of some of the other infrastructure that are there.

We just know the particular assay of genomics is a particularly expensive line item, but it's not at the expense of the others. In fact, we are just working with the IRB now in identifying some no-brainer ones that we would know that we would do that are useful to both participants and researchers out of the gate.

Ian Lipkin: So what would those comprise?

(Eric Dishman): It would hardly be, I do not want to pre-empt the input sessions that folks are going to have with this, but if you want to participate in giving advice to those, that would be a tremendous thing.

Francis Collins: Yeah, keep in mind this is a platform that provides opportunity for all kinds of additional value to be added to it, and that's what all the institute directors are now brainstorming with (Eric) about. If you have this already funded, you have these million people who are accessible for other kinds of research studies, what's your dream about what you'd want to add to this? And there's a lot of dreams going on out there.

It would enable studies, not necessarily all of them done on all one million people. You could imagine studies on a subset that could be done much more cheaply and effectively with this particular platform in place than if you had to start from scratch.

Eric Dishman: That's right.

Francis Collins: So again, if we had infinite dollars in all of us program, a lot of these added value kinds of measures, whether it's microbiomes or lots of laboratory measures or fancy environmental exposure assessments maybe could be included within the overall umbrella. But at the moment, it's going to take

most of the money we've got to set up the platform and get it ready for all of those other additional studies. Does that make sense?

Ian Lipkin: (Francis), I follow what you're saying but I'm going to say it again, because we went through this with another cohort and we have so many regrets about what we did not do. So the EHS people stress urine collection as a way to look at toxicology, and people who want to do functional analyses, via proteomics, metabolomics, are going to need plasma and serum that's been collected specifically for that purpose. That's even without talking about microbial studies.

So I'm happy to provide input on what we've done in Norway that worked and didn't work any time.

Eric Dishman: That's terrific.

Francis Collins: Appreciate that, (Ian). And I think the point you're making is very well taken, that even if we don't have the budget to do a lot of analyses of bio specimens, we should be collecting the bio specimens. Got you.

(Rick Lifton): This is (Rick). I just want to follow on to that. Certainly part of the report emphasized the desirability as (Ian) said of prospectively making sure that at time zero we collect plenty of samples to be able to go back and do further biochemical and analyte measurements. I think Vamsi Mootha made the nice point that metabolytes are beautiful integrators of genotype and environmental exposure that provide real opportunities to link these to ultimate clinical phenotypes.

And so I'm sanguine as long as you've collected the specimens at time zero to be able to go back and do specific measurements as called for later on.

(Eric Dishman): That's exactly what's being built out with the capacity of the Biobank and exactly what will start happening, at least at the outset in beta phase with real people on May 22, if all goes well. And we have been really careful not to move too forward on either genomics or these other -omics, until we have enough participants, because we are serious about participant input so that we're getting both academic and scientific input as well as what can we deliver as value to participants.

And I'll tell you aside from genetics one of their top-rating ones are things that can help them understand, you know things about their environment and their environmental situation. So it's high on both lists.

(Peter MacLeish): This is (Peter), I have a question about geographic representation. Are you going to try to make sure that the South is at least represented or maybe overrepresented? You know, if you look at disease maps, chronic disease in particular, the South is overly represented there. When you recruit participants, are you going to get people from the South, in particular rural parts of the South?

(Eric Dishman): Yes, it is one of our current weaknesses. We plan to do additional health provider organization rounds and we've publicly said that we anticipate doing that with smaller catchment areas, if you will, or smaller requirements of what these medical centers need to sign up for. The numbers were pretty large in the initial round and it meant that particularly in the South and the Pacific Northwest, there were a lot of folks who couldn't just meet the number threshold and they weren't able to get a consortium of other hospitals or clinics to be able to do that.

Both the direct volunteer mechanism as well as what we anticipate, now this gets back to budget dependency, right, of additional health provider organizations around. We have some particular gaps in the Southeast and also some gaps in the Pacific Northwest, and we can use existing fundings to fill some of those. But I think we're going to need some anchor tenant health provider organizations to really do that properly, and we have some in mind.

(Peter MacLeish): It would be nice to have a map of participants as you collect them.

(Eric Dishman): Yes, we've built that infrastructure to be able to do that, and so we can adjust, you know, both as methodologically what's working well with different communities, and also adjust based on geographics.

Francis Collins: Other comments?

Geoff Ginsburg: (Geoff) here. (Eric), thanks for this. It seems like in the ten-year period there's going to need to be some wins that the initiative will show for the participants, the research community and demonstration to Congress, and I'm looking at your trade-off questions and I'm wondering if you've identified what those wins might be and how the budget scenarios might change your ability to deliver on those.

(Eric Dishman): It definitely does have implications for that. And you're right. I had to draw, I had to sort of do a cutoff on the slide of how many swim lanes of implications I wanted to show you, but we have been working with the consortium scientists to identify and with participant feedback to identify, you know, early capabilities we want to give back to participants, and as well as you know, these are some low-hanging fruit science.

The very first science that we're going to do is publish things just about what we're learning about the recruitment process, and we're setting that up in a methodological and comparable way so that we can help share with the field, you know, these kinds of recruitment paradigms don't work.

So those road maps do change and they do force some tradeoff discussions that as we do our scientific workshops with the institutes in the broader scientific community, once we have a firmer set of the budget we'll be able to sort of constrain or expand those, the implications of that science, you know, depending on what's budget feasible.

And obviously we're not going to take no for an answer. We want to figure out, we've already got people approaching us about public private partnerships. So that question of what do we need to pay for everybody versus what might others help co-pay, to accelerate, you know, proteomics, the folks are even coming to us already. We just got to get the platform off the ground so that we can, you know, say we've got something real enough to then be able to respond to their ideas of what they're coming to us with.

Geoff Ginsburg: It was quite interesting to hear of the UK Biobank at Regeneron and Glaxo Smith-Kline entering into a relationship this past week or two.

(Eric Dishman): Yeah, (Rory) keeps telling me, "Get everybody else to pay for the most expensive items. You don't have to do it."

Francis Collins: Yeah, (Rory)'s on the advisory group so we keep hearing about what the Biobank is doing, it's been very instructive. Any other comments? Okay, thank you then. Let's move to the fourth of the four, which is the brain research through advancing innovative neurotechnologies, otherwise known

as BRAIN in capital letters. Walter Koroshetz is on the phone from somewhere in Europe, and Josh Gordon is here in the room.

Josh Gordon: Hi everyone, so I'll take you through and then Walter and I will both be available for questions. So first I guess I should also start off by thanking all the hard work that the ACD has done to help initiate and support the BRAIN initiative over the last few years.

So as most of you know, the BRAIN initiative is guided by a document that was put together by a working group of the advisory committee's director, BRAIN 2025. And that document specifies the goal of the BRAIN initiative to elucidate the circuit structure and function of the brain with a long-term goal to find out enough about how the brain works to make circuit abnormalities the basis of diagnostics and also to be able to use advanced technologies to normalize circuit function as a target for intervention for both the neurologic and psychiatric disease.

So the BRAIN initiative, the 2025 reports set aside, sorry set up seven high-priority research areas, and those seven areas still serve to guide the BRAIN initiative and serve as the subject matter of the working plan that we will submit to Congress. So the first of those areas is discovering the diversity of the brain, cataloging the likely hundreds if not thousands of brain cell types that make up the human brain, to, and I should mention also that of course that would, we're first attacking this through model systems, to do it for the human brain as well.

To develop maps at multiple scales, maps include everything from basic circuit diagrams of what brain regions project to what brain regions, to detailed maps of the, even down to the cellular and synaptic level. The third area is highlighting the brain in action, that is producing a dynamic picture of

how brain activity changes over time and with behavior and that area is predominantly trying to develop improved methods for really large-scale, huge scale perhaps monitoring of neural activity, thousands of neurons at the same time with, you know, perhaps even co-brain.

And then the next area for demonstrating causality, and I guess I should mention I'm on the third slide of the presentation, numbers aren't on the slides. Demonstrating causality, developing increasingly powerful tools to intervene in the brain in action to mimic or disrupt patterns of activity, study their effects on behavior and with the idea that one could use such technology to intervene in circuits in behaving humans to treat illness.

A fifth area is really about theory and computational tools that identify fundamental principles about how the brain works, so that we can better guide the use of the technology developed in the previous aims, to manipulate and study brain activity. And the sixth is then to apply those technologies to the human brain. So develop technology that we can use, hopefully as non-invasively as possible but invasively as necessary, to understand the human brain by studying it directly and to treat disorders of the human brain.

And then the seventh area is of course integration of all these approaches together to really inform our understanding of and ability to treat health and disease. I have the sixth non-integrated areas illustrated here in different colors on the following slide with the funding levels, historical funding levels for the beginning of the initiative in 2014. And you can see that our funding has been going up so that we anticipate spending about $190 million in fiscal year 2017.

In terms of the financial work planned for the Cures, we want to build on those numbers. Sorry, one thing I should say is the amount that we've been

spending so far is just less than the amount that the working group recommended. So in terms of a 2025 plan as currently funded, we're likely to fall a little bit short of the recommendations of the working group.

The Cures money, and this is the curve that was shown earlier, the Cures money comes in on top of a base of about $140 million to give a supplemental funding from FY17 to FY26, and you can see that curve goes up with a big bolus in fiscal year '23. So to try to smooth this out a little bit, what we've done is create a plan that includes a combination of competing grants, which is sort of new awards that are awarded in the traditional style, where we award the first year in a given year and out years are paid in subsequent years.

And non-competing awards, which is of course the out years of previously awarded grants. And then a new category, this multi-year funded category, which was mentioned earlier with regard to cancer moonshot, is where we fully fund a multi-year grant with current-year allotments. And in doing so, we do as we sort of spread out that, the boluses, smooth out everything so we keep technology progressing.

However you know with the increase of funding, particularly in years '22 to '24, really gives the advantage to harness the technologies we'll be developing through then and roll them out on a large scale across the scientific community, so we're very much looking forward to the opportunities that that provides in the latter years of the BRAIN initiative.

I had some scientific highlights but I think in the interest of time we'll skip those and we'll just say that our plan allows us to maintain some flexibility to take advantage of emerging scientific opportunities, particularly in those late years, and smoothes out the funding to make sure that the community can count on continued progress throughout the period of funding through 2026.

Francis Collins: Bravo, thanks Josh, and now both Josh and Walter would be happy to take questions and comments.

(Peter MacLeish): This is (Peter).

Josh Gordon: Yeah.

(Peter MacLeish): So the original plan called for instrumentation or technology in the first five years and then scientific questions, second five years. I don't see any mention of any of the scientific questions in this plan so far.

Josh Gordon: Yeah so the scientific questions is probably best contained in area six and seven, where we advance to the human and we try to integrate across these areas. The bulk of the funding over these first few years has been in technology development. We're beginning now to do two things which we think will get us to the scientific questions.

First and foremost is, and this was asked earlier, we're spending a considerable amount of money on training and new investigators to make sure that they're there to answer the questions that arise. The second is that we're spending also, we're beginning to spend money on databases and dissemination so that more and more investigators have access to these technologies and the data that the technologies are generating.

And over the next couple of years you'll see a transition to where previously the grants, actually we've already begun to do so, but previously the grants have really emphasized technology development and you'll see that transition to emphasizing using those technologies to answer basic questions like comprehensive maps of both model organisms in humans and turning to a

fundamental knowledge about circuits and eventually a knowledge about how those circuits go awry in disease.

So I would say we're probably a little bit behind the timeframe of five and five, but we should have five good years of that answering scientific questions by the time we hit 2026 for sure.

Walter Koroshetz: Could I just add, it's Walter here, so (Peter) we have been funding these integrated circuit grants, which are teams which use the most advanced technologies to answer questions about different circuits of interest. So in the slide where we had the different fundings and different color, that light green was the understanding circuits. So that was about $25 million in 2017 of new money.

And then in the pie chart at the end, the largest amount goes to this integrated approaches and principles, which will be these, tacks on really nailing down particular circuits.

Josh Gordon: Yeah, sorry I didn't get to that slide but was just the next to the last, the big colored pie chart, I think it's about slide nine. No, 11, sorry. And that divides the funding up instead of year by year into the approximate levels that we plan on in each of the BRAIN initiative 2025 plan areas, and you'll see the purple is the $500 million for integrated approaches and principles, which is really focused on knowledge as opposed to tools.

Francis Collins: Other questions?

Geoff Ginsburg: Jeff here, just an observation, and this is probably obvious that a cross-cutting theme with all of these initiatives is in the area of data analytics and data science, and I'm wondering if there's been any thought about any way to

either enhance the crosstalk and cross-fertilization between the initiatives or to achieve any economies of scale in those areas.

Josh Gordon: Well I think, let me answer a question you didn't ask and then answer the one you asked. The BRAIN initiative is funding lots of engineers and computational people in order to develop the techniques and experience necessary to use big data approaches. And I just pulled up a slide, I think it's slide 14 in the presentation, that shows how many people we're funding in areas like engineering and biostatistics, which is actually considerably, some of the stuff, it's more than the neurosciences.

The second question, which I think any one of us could answer is that we're having discussions at a trans-NIH level to develop a comprehensive plan for data sharing and data storage. It's probably going to take a while to get there, but it's definitely something that we're very interested in, and we think, we are, you know, we're developing, actually we have out on the street already announcements for the data storage and data sharing components of the BRAIN initiative and hopefully that will serve as one of several different examples of how to do so and we'd like to move that towards a trans-NIH basis.

Francis Collins: Yeah, Jeff, you raise a very important question and (Russ Altman) will certainly weigh in on this and the fact that the ACD has been encouraging NIH in this space for several years to wrap our arms around the data science challenges and opportunities and to figure out what we need to do both in terms of the resources that we put into it and the structure that we place around it, and the infrastructure that we need in order to achieve the kind of cloud-based data commons model that ultimately we want to get to.

There's a huge amount of effort and discussion going on about this and of course another part of it is another thing the ACD did, which is to make recommendations about the evolution of the National Library of Medicine into becoming a hub for data science. Now that we have an NLM director in the form of Patty Brennan, that has gotten underway in a significant fashion.

I will tell you, it's a topic that's occupying a lot of people's time and energy and it is complicated and sometimes stressful to try to figure out how to do the right thing in such a rapidly moving space. But I can certainly promise you, it is getting the kind of focus that you would want to see, and ultimately of course we do want to figure out how not just to do some pilots here and there but to figure out how to link up very large data-producing programs.

And that certainly includes everything you've heard about today but particularly precision medicine initiative, the cancer moonshot and the brain, regenerative medicine maybe not quite at the same scale, but there's lots of other data production efforts going on at NIH that are also really quite daunting in terms of the data sets that they are producing or have produced which need to be migrated into a place where they can be sustained.

So yeah, our attention is on this. I wish I could say "Oh, I've got a nice clean answer for you," but believe me we're working on it.

Josh Gordon: I personally can't wait until we can apply some of these brain technologies on a large enough scale that we can take advantage of the (unintelligible) cohort. I think that's going to be a wonderful period for discovery.

Francis Collins: Yeah, and I think…

Elba Serrano: (Francis), this is (Elba). And so I believe I saw a call for neuroethics as part of the BRAIN initiative, is that correct? Is it, I would think that there's an opportunity for all of these initiatives to perhaps have an ELSI-like component. Has anybody been thinking about that, or what are your thoughts in particular with regard to the BRAIN initiative?

Josh Gordon: Well with regard to the BRAIN initiative I think Walter might be best able to answer, he's been most tightly integrated, involved with the neuroethics piece.

Walter Koroshetz: Yes, so it's pretty clear right from the beginning that a lot of these technologies that are coming out will challenge some of the, some of society's norms in terms of being able to analyze brain activity to modulate brain activity. So right when the BRAIN initiative started, the president actually started a bioethics commission that looked at and gave recommendations about the BRAIN initiative.

The major recommendation was to start with integrating their ethics in the beginning, and so we have a multi-council working group that advises us on the BRAIN initiative and there's a division within that which is, the neuroethics division, this includes ethicists as well as scientists, lawyers, and we've had a number of meetings around issues, continue to do that and are trying to actually develop some kind of umbrella document to guide us going forward, and also tackling things as they come up.

So I think we're way ahead of the situation as it is now, but as you can imagine, if this is successful that I think for the medical issues it'll be easier to handle. We are certainly more concerned about the non-medical uses of some of these things.

Francis Collins: So yeah, we are keeping a close eye on that and (Elba) your question's highly appropriate. I don't know (Eric) if you want to say whether you think the TMI offers any unique ethical questions, such as return of results for instance and how that's kind of being handled.

(Eric Dishman): Yeah, I think for us, I mean on the one hand we're not funding ELSI grants on top of it because we're not funding anything at this point in time on top of it, we're building the resource. We've been having conversations within HGRI and many of the ELSI folks around NIH, just my own particular passionate area where actually I have something I can contribute scientifically.

The, so we're, we do think in particular as you start to look at the richness of data types brought together, I mean we're having to go through this but I'll tell you quite candidly with the IRB right now, we'll say "Wait a minute, what has traditionally been not risky data captured but once combined with this datatype and this data type and this data type," it's going to change the categories of risk for what you do, and you need to be able to communicate that risk.

We had a fantastic two-hour, or two-day workshop a few weeks ago in partnership with NHGRI just on the return of genetic information and we're planning some similar kinds of things with these even newer data types that we don't know what those are before we even start to develop the plan for each one of them. We, you know, are going to be working on different -omics plans but we're really trying to look at those social issues because we have to start educating people about them now, and at least have some high-level consent of them now, even though nobody knows all the answers to those as we go forward.

(Peter MacLeish): (Francis) I'd like to return to the brain.

Francis Collins: Yes.

(Peter MacLeish): I think the 2025 report was well received, and part of that was, you know, the committee that you set up, the working group consulted with the extramural community and met all over the country, and sought the input from experts to venerate those seven priority areas.

That's, you know, a lot of discussion went into that and you know the second five years or the second phase of five years or not, in terms of the scientific questions, I think there should be a similar working group to identify and consult with the extramural community as to what they think the most critical questions are that will sort of break open you know the workings of the brain. I don't see that happening quite yet, and I'm a little concerned that it needs to happen.

Josh Gordon: I think, you know, that's a really good point and we've just been engaged in discussions very recently around that exact question of whether we want to reconvene a perhaps similarly composed working group to guide us through the latter half of the BRAIN initiative, so I think you can look forward to hearing more about that in the future.

Francis Collins: Yeah, (Peter), you're right on track here because obviously whenever you try to plan something for ten years that's moving as quickly as this you're not going to be able to just sail right through a decade without coming back and reconsidering all the things that happened, you didn't expect some of the things went faster, some of them went slower, new ideas, it's a great opportunity to begin to figure out how to revisit that and to capture all the bright brains out there that helped us the first time around, and a bunch of

others as well to sort of revisit whether we have our plan for the second five years, as fully characterized as it needs to be.

So yeah, very good point. Other questions? Well hearing none, I think then we do need because this is an official part of our responding to the Congress that is consulting with all of you, we do need to take an unblocked vote about your approval of the four presentations you've had. Let me say we have listened to your comments and I think there have been some interesting suggestions for clarity, and we will take those very much under advisement and revise the text that we have and the visuals as well.

But I would like to hear now if there is a motion to accept in general the presentations for all four that we can then move them forward to the Congress.

(Peter MacLeish): So moved.

Ian Lipkin: Second.

Man: So moved, second. (Eric Goosby).

Francis Collins: Okay, is there any further discussion? Hearing none, then let me call for a vote, all in favor please say aye.

Man: Aye.

Man: Aye.

Woman: Aye.

Francis Collins: Anyone opposed? Any abstentions? Well, my goodness, I thought we were going to be struggling to pull this off by the end of a two-hour period but our speakers and our discussions and all of you on the ACD have been very efficient and very focused. So the next steps are basically we will put this all into its next iteration and we will certainly get this to the Congress by the deadline of June 11, and I think at this point we're in very good shape to put something forward that has been nicely considered and nicely reviewed, so thank you all for that.

We will meet again ACD members in face-to-face June 8 and 9. I hope that's on your calendar. Please check to be sure that it is, because we do much better when we have full attendance. We will have a lot of issues to put in front of you at that point, there's a lot happening at NIH. I won't go into it right now but I'm sure you won't be bored if you come for that meeting, and I hope you all will.

So many thanks to all of you for giving us your time here, this has been a very productive discussion. Much appreciated, please accept our thanks and we give you back 17 minutes to do something, whatever you want to. You don't get that all that often.

All: Thank you.

Francis Collins: Thanks everybody.

END