Transcript of
NIH Advisory Committee to the Director Meeting
September 5, 2014

Operator
Welcome and thank you for standing by. At this time, all participants will be in a listen-only mode throughout today's call. Today's call is being recorded. If you have any objections, you may disconnect at this time. Now I would like to turn the call over to Dr. Francis Collins.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Thank you, operator. Good afternoon everyone. This is a meeting of the Advisory Committee to the Director for National Institutes of Health. Welcome to all of you. We have two major issues that we have convened the ACD to discuss, and we will come to those in just a moment. I wanted to just take a couple of minutes to tell you about two new working groups of the ACD that have been assembled, just so that the Advisory Committee is aware of their activities, because you will be hearing more about them.

One of those is a working group focused on the Intramural Research Program at NIH, the IRP, as we call it. As you are well aware, NIH maintains a robust Intramural Research Program designed to foster the pursuit of projects beyond the scope of what is often reasonably fundable in the extramural community. And this includes the ability to start long-term research projects that change directions quickly when scientific opportunity or public health need arises, to take advantage of the largest research hospital in the world, the Clinical Center. Previous reviews of the IRP have been insightful and useful, but the last one is now 11 years old, and we thought it is time for a working group to evaluate, especially in sort of difficult budget times, the sustainability of current approaches and to identify areas of opportunity and means to enhance the uniqueness of the IRP.

This group is being co-chaired by Cato Laurencin and Larry Tabak — thank you, Cato, for your willingness to serve as co-chair — and fellow ACD member Helen Hobbs is also on this group. The group has met twice by phone already. Just this week, three members of the working group participated in a site visit to tour the NIH campus and speak with faculty members and senior leadership. And this group is charged now to report back to the ACD at its December meeting regarding its findings. So, I am sure we will have an interesting discussion at that point.

The other working group that I wanted to mention was announced in July, and that was a group charged with identifying the best path forward for the National Children's Study at NIH, and we sent you an email about that. This — the Children's Study, as many of you know, was requested by Congress through the Children's Health Act of 2000 and is currently envisioned to be a longitudinal observational study that will follow 100,000 children from the womb to age 21, with the goal being to enable an examination of the effects of a broad range of environmental and biological factors on children's health, growth and development.

The NCS has had — I think it is fair to say — a tumultuous history. A new National Academy of Sciences report from 2 or 3 months ago raised significant concerns about the design, management, and oversight, and hence we have assembled this ACD working group on the NCS to evaluate whether the NCS is feasible as currently outlined and to propose next steps based on their findings. This group is being co-chaired by ACD member Russ Altman and by Phil Pizzo, both from Stanford. Fellow ACD member Renee Jenkins is also on this group. Thank you, Renee. And thank you, Russ, for your

willingness to do the co-chairing. We have added to this additional expertise in statistics, toxicology, environmental health science, pediatrics, and other fields, and a roster has been distributed to you.

This group has met twice already, once by phone and once in person on the West Coast. They are busy at work and will be reporting back to the ACD at the December meeting regarding their findings. So again, we are going to have a busy time in December. I hope your calendars are well marked to come and spend that time helping us with these very important decisions about how best to guide NIH's path forward.

So, by way of introduction, wanted to mention those two working groups, but now to the main event. First of all, we are going to have a report from the HeLa Genome Data Access Working Group; following that, a report from the Human Embryonic Stem Cell Eligibility Review Working Group. And I want to be sure that we give time to both of them, so I am going to be kind of watching the clock here as we plunge in. But first, let's move to the HeLa Genome Data Access Working Group and its chair, Renee Jenkins. This working group has met eight times since its initiation a year ago — yeah, wow — and evaluated 30 data access requests.

This has been a truly historic means by which these requests are being considered, and as you may know, with input from the Lacks family. Renee will describe the working group's finding on four requests, and in addition, when we first set this up and worked with the Lacks family on data access, the focus was only on whole genome sequence data. We had promised to revisit that policy and determine whether we should broaden the scope to other data types.

So NIH and the HeLa working group held a workshop on May 14 with an elite group of bioethicists, bioinformatics experts, legal and scientific experts, and members of the Lacks family. You will remember an overview of that workshop was presented at the June ACD meeting, but Renee is now going to describe the working group's findings from this workshop to you today, and we will need to basically discuss and take votes. So thank you, Renee especially, but all the working group members. I am sure ACD members may have questions related to the topic, so I will ask that they pay close attention and after the discussion, we will have a chance for people to make inquiries, and then we will take a vote.

So, Renee, can I turn it over to you?

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University

Absolutely. Good afternoon, everyone. As you can see on your agenda, I have 10 minutes, so I will probably talk really fast, but I think you have the slides, and I will refer to the slide numbers as I move through the presentation. We are going to try to get through a little bit of the background, just to remind you about what the workgroup actually does, in terms of what it presents to you, to make you aware of the four access requests that we have had a discussion about and then talk about the workshop very briefly. And then we will have an opportunity to have you vote on the workshop recommendations as well as on the four requests that we reviewed.

Slide 3 again reminds you about what the guidelines are for the researchers, in terms of what they can request and what we have also outlined in terms of their criteria. For example, requestors are not to make contact with the Lacks family, and they are to disclose any commercial plans and include acknowledgment in publications and presentations. And these are the guidelines.

Slide 4. What the workgroup actually does is evaluates the requests to make sure they are consistent with the agreement. What we do following that is what we are doing today, which is, we give a report to the ACD, and then the ACD makes a recommendation to Dr. Collins. So we are reporting to you today.

Just to remind you who is on the roster, most importantly I think, the Lacks family. Veronica Spencer and David Lacks have been very involved in the discussion, and it has been really, to me, amazing for lay people to be as engaged as they are, and I think that the process works. Kathy Hudson is also part of that group, as is Russ Altman, another ACD member, as Dr. Collins told you earlier. And then we have two other experts in the area of genetics who have joined us. And then Clyde Yancy, as you remember, is a former ACD member who is also part of this group.

The criteria for evaluating are on Slide 6. The proposal has to involve research on health, medical, or biomedical research objectives. We specifically ask about the issues of intellectual property, although we have no jurisdiction over that. We just want to be notified and then, are there any plans to publish or present the findings?

Slide 7. As we progressed initially, there was a request to the applicants to have instructions in non-technical language. And it has been really trying to have them really go to non-technical language. Sometimes it looks like they just basically cut and paste what they already wrote in the application. So we are trying again, being much more explicit about what we want in those, as a result of that non-technical research summary, and they are in the "Special Instructions."

Slide 8. What we do in our review is to either identify that the application is consistent with the Data Use Agreement; that it is inconsistent with the Data Use Agreement; that it is conditional, meaning the issues with the application can be resolved internally and we can basically say go forward once these are satisfied; or it is pending, meaning we cannot — we want to hear it again, that we are not able to make a determination at the time we initially review it.

So, the requests that are currently before you. First of all, just to remind you, we have had 30 requests altogether; 21 were approved by you, one was disapproved. There are still four that are pending, and we are reporting on four today. Just for an FYI, 10 of the approved requestors have downloaded the data.

So, as you see here, here are, on Slide 11, are the four projects, and Russ Altman has agreed to briefly tell you about them. Russ, are you there?

Russ B. Altman, M.D., Ph.D., Professor, Bioengineering, Genetics, and Medicine, and Director, Biomedical Informatics Training Program, Stanford University
I am.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Okay.

Russ B. Altman, M.D., Ph.D., Professor, Bioengineering, Genetics, and Medicine, and Director, Biomedical Informatics Training Program, Stanford University
Would you like me — I can quickly go over them. I think the summaries are pretty good, and I want to take a minute to thank the staff, including Dina Paltoo and everybody else who really make this

committee go very smoothly and often create descriptions that are much better than the investigators about what the investigators plan to do, somewhat not surprisingly, I am afraid.

So we have — very quickly, in fact, I prefer to ask questions just in the name of keeping time, but the first one was a study from Berkeley where I think the key point is that they are looking at multiple forms of messenger RNA, and they used the HeLa cell line as the model system. And therefore having access to the genome allows them to tell if the mRNA differences that they are seeing are because of differences in the genome or because of editing or other splicing or other events that have happened to the mRNAs after transcription. So, again, we looked at that, we thought that looked good. I am going to keep — I will forge ahead if that is okay, Renee.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Please, mm-hmm.

Russ B. Altman, M.D., Ph.D., Professor, Bioengineering, Genetics, and Medicine, and Director, Biomedical Informatics Training Program, Stanford University
For the second one, from the University of Washington, they are interested in a 3-D structure of DNA in the nucleus. They have Hi-C data, which is a type of next generation sequencing combined with other experimental assays that gives them basically linkage information that says, this part of the genome is close in three dimensions to this other part. And the data that they have is on the HeLa sequence, and so for interpreting that data, it is absolutely critical, and we agreed, to have access to genomic data.

The third one, from the University of Pittsburgh, is very interesting, looking for what the effects of viral infection on genomes are. And so, for example, we know that many cervical cancers, as I am sure many of you know, are associated with HPV infection, and so they want to look at a metagenomic survey of the genome to look for the presence of DNA that might be from infectious agents. And of course, HeLa is a great model system for this because of the likely etiology, although not proven, of that cancer in the case of Henrietta Lacks.

And finally, and forgive me for going so fast, there is a proposal from Vanderbilt that is interested in what the effects on the peptides that are displayed on the surface of cells before and after virus infection. And so they are infecting HeLa cells with vaccinia, and they are comparing the before and after of the displayed peptides, and they want to have the genome in order to tell what of those peptides are encoded and where in the genome, to try to unravel how this viral response might be managed.

So, I think I will stop there. Of course, it is not enough to really appreciate the science, but I can tell you that we went through these, and we thought they were consistent with the Data Use terms that Renee reviewed previously.

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
This is Bob Horvitz. I have a question, and that is, on Slide 11, there is one aspect of information that is not included but was included in the other material we were sent, which is namely the name of the investigator. Is there any reason going forward we couldn't include that in a slide like Slide 11?

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
We would be happy to do that, Bob.

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
I think that could be helpful, in some circumstances.

Russ B. Altman, M.D., Ph.D., Professor, Bioengineering, Genetics, and Medicine, and Director, Biomedical Informatics Training Program, Stanford University
And just real quickly, the University of California, Berkeley, is Steven Brenner; the University of Washington is William Noble; the University of Pittsburgh is James Pipas; and the Vanderbilt investigator and University of Texas, El Paso, investigator is Charles Spencer.

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
Great.

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
This is Ian, just following up on Bob's point. I have to recuse myself for the Pitt application because Jim and I worked together.

[Unidentified]
Okay.

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
So it is important to have those names.

Russ B. Altman, M.D., Ph.D., Professor, Bioengineering, Genetics, and Medicine, and Director, Biomedical Informatics Training Program, Stanford University
Good point. Thank you.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Very good. Very good point, thank you so much. Russ, thank you very much.

Christopher B. Wilson, M.D., Director, Global Health Discovery Program, Bill and Melinda Gates Foundation
And Chris Wilson. I recused myself from the University of Washington one because I have a consulting relationship on one of their committees, and I also heard Bill Noble present this about a week ago, so I am biased.

[Unidentified]
That's interesting.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Thank you, anybody else have a recusal that you would like to mention before we vote on these?

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
I would just make the argument that knowledge of the science shouldn't be a reason to not participate. But, if there is a conflict, then it is fine.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Okay, totally agree with that Bob, thank you. Otherwise, we may as well all go home.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
So now, we were going to wait until the end to vote, okay.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Fine.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
All right, so we are going to proceed with the — what you need to be aware of for the workshop. And we are on now to Slide 13. As you see, the workshop focus was to really evaluate policy as to whether we should apply prospectively to the guidelines to any other HeLa genome data types. And it was a one-day meeting. You can see here are the workshop participants. And you may also note that the Lacks family, I think, had four members that were at the workshop, and they were very engaged in the discussion. There were not only scientists who were working with HeLa cells, but also EpiSys that gave really important presentations. So, I think it was a very worthwhile and informative meeting. I don't know, Kathy, do you want to say anything else about it?

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
Mm-hmm. Go ahead.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Okay. Great. Okay. So, the agenda overview again was looking at future considerations around open-access, issues around the scientific value of the HeLa genomic data, what privacy risks exist, what ethical implications there are of open versus controlled data access and also applying the HeLa genomic data policy to other genomic data types.

And the Lacks family expressed themselves specifically and felt as though their desire was to have scientists have access to the HeLa genomic data. They did not want to add any policy issues that would delay or halt the progress of the science with the HeLa cells, but they did want to be informed about the scientific developments associated with scientists who use the HeLa cells.

So, the outcomes of the workshop are on Slide 17. And there was not much enthusiasm, which is a nice way of saying it, for expanding the policy. There was very active discussion about that. There was also expressed that the HeLa genomic data beyond whole genome sequences do not need to be kept in controlled access. There was a discussion about the HeLa cell research collection, and I think we are not going forward with that because of the amount of effort and time that would be necessary to do that. And then the research symposia, which there was some enthusiasm for, and so I will put that together in a recommendation that the workgroup had. And information sharing with the Lacks family, which I think

is occurring and would actually, if we accept a research symposia going forward, would be an additional opportunity for them to be aware of that.

So on Slide 18, you see that the privacy considerations are not significant enough to outweigh the scientific and public health benefits of adding other genomic data types to limited access. And the workgroup also endorsed a periodic symposium in association with the current national — a current national scientific meeting, as opposed to having a specific meeting that is generated by NIH. Okay. So the next steps are to make a recommendation to Dr. Collins from the ACD and then the NIH would consult with the Lacks family going forward, before Dr. Collins would make a final decision. Okay, and so I think that is the end of the presentation. Am I on time?

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
You are doing great, Renee, but let's hear if there is discussion from the ACD members. Again, remember how this works, working groups present you with findings. You then have the chance to discuss, and then we will have a vote for you to make recommendations. Then I receive those, consider them — in this case, discuss them with the Lacks family — and make an ultimate decision. But are there discussion points?

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
What we have put up, as you look at Slide 21, it once again has the list of the data access requests.

Peter R. MacLeish, Ph.D., Director, Morehouse School of Medicine Neuroscience Institute, Morehouse School of Medicine
Just a comment. I am so impressed that the family is interested in the science, and I think that every opportunity should be taken to commend them on that.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Totally agree with you, Peter, and I believe Jerry Lacks is listening in to this call, and Jerry has been remarkably dedicated to this effort. And we will continue to benefit from the input from her and other Lacks family members. So maybe, Renee, we will need to take two votes after people have a chance to discuss; perhaps one on the data access requests—

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Mm-hmm.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
—and once on the workshop findings, but maybe we could start with the data access requests.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Okay, do we need a motion from—

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
This is Ian; I move to accept.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Great. Do we have a second?

Lisa A. Cooper, M.D., M.P.H., James F. Fries Professor of Medicine and Director, Johns Hopkins Center to Eliminate Cardiovascular Health Disparities
Second.

[Unidentified]
Yes.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Okay. All in favor?

Multiple speakers
Aye.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
All of you. Any opposed?

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
And we noted the people who are recused on the basis of institutional conflicts. Were there any abstentions, not counting the recusals we already heard about? Okay.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
All right, so we—

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Now to the workshop—

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
—yeah. The second vote would be to endorse or to approve the recommendations that are on Slide 18—

[Unidentified]
Mm-hmm. Right.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Now 22, I think, is sort of the way it has been put forward for—

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Oh, 22, okay. Dina has it all organized, and I am just not paying attention. Okay. All right. So, no change to the HeLa genome data policy, but to recommend that the NIH should hold a periodic special session at a national scientific meeting focusing on the research utilizing HeLa cells. Do I hear a motion?

Russ B. Altman, M.D., Ph.D., Professor, Bioengineering, Genetics, and Medicine, and Director, Biomedical Informatics Training Program, Stanford University
So moved.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Do I hear a second?

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
Second.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Any discussion? Hearing none and no one abstains. All right, then we are—

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Ask for a vote—

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
All in favor?

Multiple speakers
Aye.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
Okay, and none opposed. Okay, kind of biased way of asking.

You should see your faces, I mean really. All right. Okay.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
All right. Thank you, Renee.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
You are welcome.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
That is fantastic, and I will consider your recommendations, and I will consult with my staff, and in the case of the workshop, the Lacks family, before I make any final decisions. Jerry, thank you for being — listening in, and much praise for Renee who has ably lead this effort over this year with those eight meetings and really unprecedented series of discussions that I think have really brought great credit to the working group, in terms of how you conducted business. So, many, many thanks.

Renee Jenkins, M.D., Professor and Chair Emeritus, Department of Pediatrics and Child Health, Howard University
And I think Russ really underscored the fact that internally, it is just a great group and they really prepared for everything, so thank you for giving me the opportunity.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
And since Renee is scheduled to rotate off of the ACD at the end of December, we thought we ought to think about succession planning. And so I am happy to say that an ACD alumnus, who is also listening in, Dr. Clyde Yancy, has agreed to co-chair the working group with Dr. Hudson when Renee rotates off at the end of December. So Clyde, thank you for your many, many contributions to NIH; you are about to add another one. That is much appreciated. And we will have another ACD member also join the group, after we have a chance to be sure that it is going to work out for that individual.

So, without any further ado, I think with remarkable good timing here, it being almost exactly 3:30, we should move on to the next topic, which is the report from the Human Embryonic Stem Cell Eligibility Review Working Group. Jeff Botkin, are you on the phone?

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
I am here.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
And let me say how grateful I and others are to you for your role in chairing this group over the years and really appreciate your joining us now to present a couple of issues that you want the ACD to consider. So I will turn it over to you. I think Anne Lyerly, who is a member of the working group, is also on the phone and Jeff Murray, a former working group member and ACD alumnus, I believe is also on the phone, at least I hope so, no?

Anne Drapkin Lyerly, M.D., M.A., Director, Center for Bioethics, University of North Carolina, Chapel Hill
I am here. This is Anne.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
And Ella is here.

[Unidentified]
Ellen.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
And Story Landis also is in the room with us and Ellen Gadbois. So we have lots of people who have spent a lot of time working on these complicated issues. But Jeff, let me turn it over to you.

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
Great, thanks Dr. Collins. And my thanks to Story Landis and Ellen Gadbois for the great support they have provided us for this meeting and really consistently over the years. So, my thanks. So I am on the second slide now and brief overview of what we are going to do with this part of our presentation. We are going to talk just briefly about the guidelines that we are working under, present then a single line that we have had the opportunity to talk about on several occasions in the past, present to you our working group analysis for your consideration, and the open it up for your further discussion and vote.

I am looking now at the third slide, and this is a list of our working group members. So my thanks to this group, which has really proven to be a wonderful collaboration with some just terrific people.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
And I should have said thanks to Cato at the beginning, who is also a part of this group, much appreciated.

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
Yeah, and Cato has been involved with this particular case discussion, so he will be a help if questions come up about how we were thinking about this issue.

Cato T. Laurencin, M.D., Ph.D., Albert and Wilda Van Dusen Distinguished Chair in Orthopedic Surgery, Institute for Regenerative Engineering, University of Connecticut
Absolutely, thanks.

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
Dr. Collins mentioned Annie; Dr. Annie Lyerly is on the line, too. She is the primary reviewer for this particular application, so if we really get into the weeds, hopefully Annie can help us out with that. So next slide, number 4.

This is a brief summary of where we have come from and what the standards are here in effect, since 2009. So stem cells must be derived from embryos created by IVF for reproductive purposes and no longer needed and donated by individuals who have given their informed consent. So the key thing here is that embryos cannot be created for research purposes. They must be left over from couples who no longer need them for their reproductive planning.

The working group uses so-called "Section IIB criteria." So all applications that came in after the implementation of the new guidelines in 07/07/09 have to fulfill IIA criteria, and those are reviewed internally at the NIH. We review IIB criteria, which are lines created before that period of time, to assess the ethical conduct of investigators in obtaining those lines.

So I am looking at Slide 5 now. Here are the IIB guidelines. So the ACD working group will take into account principles of Section IIA; those are the criteria that must be met for the newer lines since 2009. We take into consideration the requirements in the Common Rule. And then there were several points to consider: whether the couple was informed of other available options pertaining to the use of the embryos, whether they were offered any inducements for the donation and whether they were informed about what would happen to the embryos. So the application today is being considered under these IIB criteria.

So slide number 6. This particular application is a resubmission now from NeoStem, but was formerly called California Stem Cell, Incorporated. So, you will see the designation CSCI on these slides. This was from an embryo that was frozen and derived in 2006 from a couple in California. So this is the third ACD discussion of this particular line.

There is a lot of information on the next slide here, number 7, so I am going to walk through this fairly quickly, and we can come back to the details if folks have additional questions. So we first looked at this application in June of 2012 — or the ACD did — and there were concerns about several aspects of the application. The original consent form that was signed by the couple lacked any information about their ability to withdraw prior to the time in which a stem cell line was derived or prior to a time at which the materials were de-identified. And that is one of the IIA criteria.

There was also what we considered to be exculpatory language in the consent form, and it indicated that once the couple had signed that form that they would lose control over what would happen to the embryo. That is inconsistent with federal regulations, and it sort of augmented potential confusion around their ability to withdraw the embryo until the time that a stem cell line had been derived. We also could not verify that a procedural document that included information about the couple's ability to withdraw was in effect at the time of the donation.

So we had made a recommendation to the ACD or our finding to the ACD was for not — disapproval, and the ACD accepted that recommendation, and the NIH disapproved the line. Then in December of 2012, the applicant submitted attestation from an embryologist that indeed the procedural document was in effect. Nevertheless, our working group remained uncertain that the rights of the donors had been adequately protected, and we did not come forward — we did not change our recommendation at that point.

So now Slide 8, please. So today what we are talking about are two new consents from the same couple. The couple was asked to sign a second consent that we will talk about in a little bit of detail here in a minute, in July of 2013. And here is the heading; this middle bullet is the heading that is on top of that consent form, "Consent to Affirm Your Willingness to Allow the Use of CSCI4, Embryonic Stem Cell Line Derived From One of Your Embryos, in NIH Funded Research and to Affirm Your Willingness to Allow the Line on the NIH Registry."

They recognized that this new consent didn't really fix the problems of the original consent. Nevertheless, the hope was that it would express the couple's willingness to have the sign — the line listed on the NIH Registry and then used subsequently in NIH-funded research, which is really the decision going forward at that period of time.

Several concerns about that second consent from our working group and the first bullet here includes fairly lengthy language that was included in the background information of that consent document. I won't read that whole thing, but I will just highlight a couple of the elements where it says that millions of dollars have been employed in this research showing huge promise for addressing the unmet medical needs of tens of thousands of Americans. And as I will mention in a minute, I think our concern was that was perhaps over-promising or excessively optimistic in terms of the near-term benefits of the decision they were making.

There was a comment about the only risk being the loss of confidentiality, but also particularly problematic for this second consent is the third bullet where it says, "your participation in allowing the

line to be included in the NIH Registry is voluntary; you may decide not to participate or you may leave the study at any time." The next slide, please.

So our analysis of this second consent, first of all, posed a problem for us because we had not really established any formal guidelines for dealing with second consents; that is, consents that had been obtained after the embryo had already been destroyed and the line had been created. So we had to grapple with somewhat new territory for us. A particular concern highlighted in the second bullet is that language about their ability to withdraw. Now I think our suspicion, or at least my suspicion was, that is probably boilerplate language that existed in some informed consent template that they simply left in.

But from our perspective, it didn't seem to make any sense. What did it mean to offer the couple the opportunity to withdraw their line from the research? Did that mean remove it from the registry? Did that mean if they had changed their minds, that somehow the NIH would or others would try to pursue anybody who was conducting research with downstream cells? It did not seem like it was, in fact, a feasible or reasonable option to offer this couple. Next slide, please.

So here is really our analysis. We felt with the second that the claims of scientific progress and impact really put a fair amount of pressure on the donors to agree to this new opportunity or to sign the new consent form. On the other hand, the couple had signed two consent forms at this point saying that they were willing to have their line derived from their embryo to be used in stem cell research, so we didn't want to deny them the opportunity to contribute to science if, in fact, that is what they were committed to. Nevertheless, we voted unanimously to present a negative finding to the ACD again on that line and that did not actually come up for ACD vote, since it didn't change the status of the line at that time.

So the story then proceeded on to Slide 12 here, which is a third consent document. So this is the third one signed by this same couple, submitted to the NIH in June of this year. I won't read the whole heading there, but it is highlighted in the center where they include in the heading greater clarity about their ability to withdraw, and basically telling them, they don't have that ability. So with that clause it says, "with the understanding the cell line cannot be withdrawn once it is distributed to NIH funded laboratories." And that is highlighted in the text here in the third bullet, "it will no longer be possible to withdraw consent for use of these cells for research for the treatment of others." In addition, the language that we had concerns about that had seemed to be over-promising scientific progress was eliminated from this third form.

So, our discussion then at the working group level was long and fascinating. Some members were willing to accept the third consent, saying we now have three different documents that this couple has signed indicating their interest in contributing to stem cell science, and that although the consent process was significantly flawed in a number of ways, a number of the members did not want to deny the opportunity for this couple to contribute to the scientific enterprise.

On the other hand, some members were concerned that the second and third consents really did not remedy the shortcomings of the first consent. Most of what we deal with with the committee is people's decision to contribute their embryos for stem cell derivation, and I think the feeling for those workgroup members was that that process was flawed, and folks were not making a fully informed decision at that point, then the second and third consents didn't fix those fundamental problems.

So, our final vote then. Unusual for our working group to be split, but we were split. We had ultimately four of our members who were in favor of suggesting that the ACD recommend approval of the line and

three who continued to hold the position that it was not appropriate to approve this line and were recommending a negative vote in that regard. So, let me go ahead, and stop there, and see if there are any questions for me or any questions that Dr. Lyerly or that Dr. Laurencin might help with.

Russ B. Altman, M.D., Ph.D., Professor, Bioengineering, Genetics, and Medicine, and Director, Biomedical Informatics Training Program, Stanford University
This is Russ Altman; I have a question. Thank you for a very cogent summary of the history, which is quite remarkable and I am — as I sit here, it is one of two situations. It is either donors who really, really want to make this contribution, and you could imagine very deep-seated reasons why they would want this to happen. And you could imagine a frustrated couple who just keeps trying with their colleagues at the company to do something that makes it perfectly clear that they really want this used. Or, you could have people at the company who are extremely motivated to have this cell line approved and who have a relatively compliant couple who are willing to do this because they really perhaps don't care as much, but have some personal connection with the company. I am wondering if you have any data on which of those situations; are we dealing with a couple that is just desperately trying to get their former embryo to be used?

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
Yeah — this is Jeff — I would say that nicely articulates the — our challenge here and we, of course, haven't had any direct interaction with the couple. And so all of the knowledge we have about that couple has come through the company and through these consent forms. So I don't think we have a good answer to an excellent question. I don't know, Annie, do you think — is that a fair statement?

Anne Drapkin Lyerly, M.D., M.A., Director, Center for Bioethics, University of North Carolina, Chapel Hill
I would agree with that. I would also say I think that the length of this process suggests that there is a very motivated research group or scientist at the other end of the spectrum, although I don't know that to be true. I think there is a suggestion given how long this process has been and all of the different ways in which approval has been — all the different ways in which they have seeked approval.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Jeff, Ellen Gadbois has information here that might be relevant about the relationship between the company and the couple. Ellen, can you—

Ellen Gadbois, Ph.D., Office of Science Policy, Office of the Director, National Institutes of Health
Sure, our understanding is that the company does not have a direct relationship with the embryo donors. They don't know their identity, so the second and third consents were done through the IVF clinic, who has the link between the stem cell line and the embryo donors.

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
I am not sure that the question is really all that relevant in part because it is so difficult to answer, but I mean, independent of that, we want a policy that is going to be sensible and consistent. And in either of the two cases that were painted, the answer might well want to be — we might want it to be the same answer in either case because the objective facts that are most relevant, which is do the parties involved understand and agree? Whether they are agreeing because they are driven or whether they are agreeing because they don't care enough to disagree with someone who wants something else, I am not sure is all that central. But since what has been said, I think makes this particular case may be easier,

because we can diffuse it a bit. We may not have to deal with that, but I just don't see that it is necessarily a key issue.

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
I'd like to follow Bob's point — this is Ian. My major concern is to ensure that we truly have informed consent without any undue pressure, and as long as that pertains, I would be on the side of the "for" vote. My concern is slightly different and larger, and that is, there is a lot of language here about the fact that one can do all sorts of things with these lines without informed consent, as long as it is not federally funded research. So my concern is if something doesn't somehow get watched in advance, and then we have to play this catch up game at the end. So, even if we approve this, there should be very clear effort to try to ensure that something like this doesn't get to this stage again.

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
One question in that context, is there an opportunity for us, i.e., NIH working group, et cetera, to interact earlier in the process to help guide what an informed consent should be?

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
So could I just — this is Story Landis, and I was involved in the generation of the stem cell guidelines in 2009, and the problem that we ran into was that once those guidelines were put in place, every submission we have had since then where the donation was made after, absolutely meet those guidelines. So—

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
Yeah, okay.

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
—we have completely cleaned up this process.

[Unidentified]
Great.

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
This embryo was donated in 2006, 3 years before those guidelines were in place and so we have tried, when we put these guidelines together, we tried by the creation of the IIB criteria to recognize that the policies before the guidelines were put in place may not have dotted all the I's and crossed all the T's. So we do not see consents like this anymore, and I would tell you that we have not had new cases that have come before the ACD Working Group from embryos donated significantly before these guidelines were put in place.

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
Right, Story, all of that is clear. I guess to focus my question, there was a second resubmission that didn't have satisfactory language that was in 2012. And so my question is, if something like this does happen, at that point is there a way to interface?

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
And Bob, this is Kathy Hudson. It's a great question and in fact, after the second submission, there was an interaction and Story and Ellen and I had a conversation with the company in order to make clear what the issues were. And so the response in the third consent really is, in part, from that interaction.

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
So there was, after the second, but not after the first. But presumably going forward, others would be helped in a similar way.

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
Yes, if there were others who had lines that, where the embryos had been donated before. But I would tell you, I think we are very close to this ACD working group being out of business for lines that — for embryos that were donated in the U.S. They also will deal with embryos donated overseas, and to be honest, we have not had cases recently that fit under that umbrella.

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
We did have the Chinese line—

H. Robert Horvitz, Ph.D., Professor of Biology, Massachusetts Institute of Technology
Yeah.

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
Yeah, but that was a year plus ago.

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
Yes.

[Unidentified]
Well, with respect to China, there is a very large stem cell program, so we might—

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
Yes, but they don't seem to care about whether or not the lines are registered on the NIH Registry, so we do not get—

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
Applications.

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
—we don't get applications for listing on our registry.

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
But that's — let's say an investigator wants to use a line that is not on the NIH Registry. Don't we need some sort of informed consent to make sure that that is an appropriate use of the line?

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
They can't do the—

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
They can't use that—

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
—research with NIH funds, period.

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
They can't be, okay. That is my question.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
That's the Obama Executive Order.

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
Great.

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
Other discussions?

Anne Drapkin Lyerly, M.D., M.A., Director, Center for Bioethics, University of North Carolina, Chapel Hill
Well, I guess I want to add, just sort of to emphasize the points that — this is Annie — that were made in the summary. There was a section of the working group that was concerned that re-consenting the donors wouldn't redress meaningfully the failures of the initial informed consent. Because at the point that somebody is donating their embryos for stem cell derivation, they have other options available to them.

The point at which these individuals were being informed of the possibility of being on the Stem Cell Registry, they had already donated their embryos; those other options were not available to them, so they were morally and experientially in a different place. And so I think the big question for our group was whether it was appropriate to consider re-consent as a reasonable process. And so maybe that is understood, but I think that that's one of the central differences on the committee was whether or not that this could serve as something that could reassure us that this was respectful of the donors.

Cato T. Laurencin, M.D., Ph.D., Albert and Wilda Van Dusen Distinguished Chair in Orthopedic Surgery, Institute for Regenerative Engineering, University of Connecticut
Yeah — hi, this is Cato Laurencin — the other issue, and I think that there were variable levels of concern about this, was the concept of a slippery slope of being able to — if one is able to re-consent, whether other companies might come out of the woodwork with their — with donors that had not been properly consented and bring — to try to have them re-consented.

And obviously we know now that the instructions are there and people have been given the instructions, in terms of what should be in the consent form, but are there companies that didn't even try to propose something to the NIH because of the fact that they knew that they didn't properly

consent the person — the donors in the beginning and didn't even take a moment to think about coming to NIH but now may go back and search out those individuals to re-consent them. I believe that some felt that that was not an issue and shouldn't be an issue, and others on the committee felt that that was an issue. And that was a slippery slope issue that was there, and I think that was one of the other reasons why there was a split in terms of the group with a thin majority now voting on this case to move forward.

Richard P. Lifton, M.D., Ph.D., Executive Director, Yale Center for Genome Analysis
This is Rick Lifton. I appreciate all of these considerations and the part that I am struggling with is this point about how deficient was the first consent? And are we viewing this critically from a perspective in 2014 that is very different than we would have looked at this in 2006 or that the company looked at it with in 2006. So where I am struggling is trying to decide how compromised the first consent was to try to understand how significant the repairs that have been made subsequently are.

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
Yeah — this is Jeff — and I guess I would say this is an application that the working group felt on several occasions had a couple of pretty significant problems with it. And it wasn't that there was one thing that was sort of clearly a deal killer, but there were — the withdr — absence of the withdrawal language in their original feedback to the committee that they had no documentation about withdrawal. And the subsequently coming forward with more information later once we had disapproved the line, in addition to a number of other errors, didn't give us strong confidence that this was a group that had all of their ducks in a row, if you will, at the beginning, and that we felt that there were enough problems with it that the group was unanimous in its original recommendation to — for a negative finding. So—

Richard P. Lifton, M.D., Ph.D., Executive Director, Yale Center for Genome Analysis
But — so I get that, but the question is, for a consent form in 2006, before the guidelines were drawn, saying that it didn't meet the current guidelines I think is perfectly reasonable. And the question is, how egregious were the errors in general consent that we would say that they can't — they would be ineligible to be remedied?

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
So, this is Kathy Hudson. I want to make a couple of points just based on the experience — and maybe Story and Ellen can chime in — of the kinds of consents that have been reviewed. And these are consents again that were obtained in advance of the guidelines being put in place. So, there were no guidelines, and people were presumably doing their best and the language about "you may withdraw at any time" really is boilerplate language and was probably included in error.

I don't know how much that ends up influencing research participants or prospective participants in terms of their agreement to participate. But there have been consents with language about "you can withdraw at any time," or "you may just withdraw," or very similar language, that have been approved by the working group and approved by the ACD and the NIH Director. So, there is an issue of fair — maybe not fairness, but at least consistency of our behavior that I think we need to be mindful of.

And the other is that there are consents where the consent is for use in research, full stop, so there is nothing more specific that is being provided to these donors than research. In this case, the donors are very well informed about exactly what the use is that is going to be made of their stem cell lines, and I think that that should be taken into account as well. And while the company may have not gotten this right the first time, or even the second time, I think that the couple has been very consistent in

expressing their desires. And it gives me pause to sort of second-guess what they have indicated as their wishes.

Huda Akil, Ph.D., Gardner Quarton Distinguished University Professor of Neuroscience and Psychiatry, The Molecular and Behavioral Neuroscience Institute, University of Michigan
So, hi, this is Huda. Can I ask a quick question about how much feedback is the couple getting? For example, if we say these stem cells cannot be used going forward, does that have to get back to them?

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
Yes.

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
Uh.

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
So, the Registry is public.

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
Public.

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
They could go and check, and in fact, they could even be listening to this discussion because this was put in the Federal Register and—

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
And they know the name of the line because it is in their consent.

Story Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health
—they know the name of the line.

Huda Akil, Ph.D., Gardner Quarton Distinguished University Professor of Neuroscience and Psychiatry, The Molecular and Behavioral Neuroscience Institute, University of Michigan
Okay, so it does, we do need to consider, this is not going into some pool and sometimes people know and sometimes people don't know what happens to their contributions and samples. But this is a particular case where it is very important to be mindful of what we think their intent and their degree of determination was about having these lines being used.

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
That's right.

Huda Akil, Ph.D., Gardner Quarton Distinguished University Professor of Neuroscience and Psychiatry, The Molecular and Behavioral Neuroscience Institute, University of Michigan
Is that a fair conclusion?

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
Yes.

Huda Akil, Ph.D., Gardner Quarton Distinguished University Professor of Neuroscience and Psychiatry, The Molecular and Behavioral Neuroscience Institute, University of Michigan
Okay.

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
Is the committee convinced that this couple does want to donate these lines?

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
We never know with consents, right, so they have signed the consent and we don't try to do that in research consents usually to then do a — yeah — unless we are doing research on consents.

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
But if we assume that that is what they really want to do—

Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, National Institutes of Health
Mm-hmm.

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
—it is not as though this is a renewable resource and people can go back and say, well, we didn't get the consent properly this time, but you can donate embryos again. I mean, this is a one-shot opportunity. So if we truly believe this is what they want to do, and we think the consent is appropriate, I would be in favor of supporting the "for."

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
So, I am mindful of the time, because I know we only asked you all to hang on for an hour and Jeff, you are moderating here, I don't know if you are ready to suggest calling the question.

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
I don't have any additional information to provide and so I guess I would say, unless ACD members have other key comments that they want to contribute, then perhaps it is time.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
So do you want to call for a motion?

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
Yes.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Someone care to make a motion?

W. Ian Lipkin, M.D., Director, Center for Infection and Immunity, Columbia University
Ian, I move to approve.

[Unidentified]
Second.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
More discussion? Okay, I guess we can try for a voice vote. If it turns out that there is significant split, we will do a roll call, but first of all, all in favor of the motion, please say "aye."

Multiple speakers
Aye.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
All opposed?

Harlan M. Krumholz, M.D., Harold H. Hines, Jr., Professor of Medicine and Epidemiology and Public Health, Yale School of Medicine
Aye.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Well, that would be a nay, but—

Harlan M. Krumholz, M.D., Harold H. Hines, Jr., Professor of Medicine and Epidemiology and Public Health, Yale School of Medicine
Nay.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
Okay, I heard one nay. Any abstentions? Okay, Jeff, I think that very much gives an outcome for your very thoughtful discussion. Thank you everybody. This is a really complicated issue and no doubt, the complications are clear by the fact that our working group, who has labored long and hard on this, remained in a circumstance of not being entirely clear what the right answer is. Again, I am taking this under advisement; that is how we do this. I will contemplate the thoughtful discussion we have had and make a decision, but I really appreciate the time that has been put into this by all of you. And again, especially thank you to you, Jeff.

Jeffrey R. Botkin, M.D., M.P.H., Chief, Medical Ethics, University of Utah School of Medicine
Thank you.

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health
And the members of the working group who have gone through this several times. And I think it is actually, somebody could write a dissertation about this one, and maybe they will. Okay, I think we are at closure, other than my needing to remind the ACD members to sign and date the conflict of interest form that was provided on your ShareFile site and either email it to Gretchen or fax it to the number that is provided. And otherwise, we would like to wish you a good weekend and look forward to seeing all of you in person in December where, as I said at the beginning, we are going to have a very busy meeting, so please plan to be here for the entire thing and be ready to focus on some very important issues.

So many thanks everyone. We are now adjourned.

Multiple speakers
Thank you.