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INTERAGENCY AUTISM COORDINATING COMMITTEE

SUBCOMMITTEE FOR
BASIC AND TRANSLATIONAL RESEARCH

STRATEGIC PLAN QUESTION 2 PLANNING GROUP

CONFERENCE CALL

FRIDAY, NOVEMBER 8, 2013

The Strategic Plan Question 2 Planning Group convened via a conference call at 1:30 p.m., Susan Daniels, *Executive Secretary*, IACC, presiding.

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PROCEEDINGS:

Operator: Thank you for standing by. At this time, all participants will be listen-only throughout the conference. The call is being recorded. If you have any objections, you may disconnect at this time.

Now I would like to introduce Dr. Susan Daniels. You may begin.

Dr. Susan Daniels: Thank you. Welcome and good afternoon to all the listeners on the phone and to the IACC members and our invited guest participants today. We are very pleased that you can join us for this conference call of the IACC Strategic Plan Update Question 2 Planning Group. This Group is going to be looking at Question 2 of the Strategic Plan, which is about the underlying biology of autism spectrum disorders: How can I understand what is happening?

And we're going to talk today about progress that's been made toward meeting Strategic Plan Question 2 objectives in terms of advances in the field. And we're also going to talk about progress made toward meeting the aspirational goal, which

is to discover how ASD affects development, which will lead to targeted and personalized interventions.

So to begin the call, I'd like to just take a roll call so that everybody who's listening in can know who's on the phone.

So the members of this Group are Walter Koroshetz. Are you here?

Dr. Walter Koroshetz: Yes, I'm here.

Dr. Daniels: Thanks.

Alison Singer?

Ms. Alison Singer: I'm here.

Dr. Daniels: Lyn Redwood?

Ms. Lyn Redwood: Here.

Dr. Daniels: Kevin Pelphrey?

Dr. Kevin Pelphrey: I'm here.

Dr. Daniels: Carlos Pardo-Villamizar?

Dr. Carlos Pardo-Villamizar: I'm here.

Dr. Daniels: Nancy Minshew?

Dr. Nancy Minshew: Here.

Dr. Daniels: And David Amaral is not going to be able to join us today, but he will be at the workshop next week.

For those of you who are listening on the phone, the materials for today's call are up on our Web site, the IACC Web site, under “Meetings and Events.” And there's a special link for the “Materials” so that anyone who's listening can follow along.

So the first thing that we're going to do today is we're going to look at the materials that I provided to you. I emailed them to you, and then they're up on the Web for those who are listening.

We have a table that was really just provided as background, and it really was the focus of the previous call, which is the Cumulative Funding Table that shows the alignment of funding across the different years in each of the objective areas of the Question 2 part of the Strategic Plan. And it gives you an idea of what was funded, how many projects.

And we actually, on the last call, had project data in tables that we provided to the Committee members. And that's all on the Web. And in this table, we also have some live links for the 2008 through 2010 data so that people could see the

actual projects.

And the members of the Committee who are on this Planning Group made some initial determinations about the progress that's been made on these Strategic Plan objectives in terms of the funding. And so the summary of what the Planning Group came up with on the previous call is in the next table that is called the Conclusions Table that you have in your attachments that I sent to you.

And this table shows you all of the Strategic Plan objectives for Question 2 -- I believe there are nine of them -- and with a brief summary of what was discussed on the previous call. And the goal of today's call is to try to expand upon what was discussed last time, to really understand what has been happening in the field that we need to know about -- that the Committee needs to know about -- to understand what they might need to do in terms of updating the Plan and to assess the progress that's been made on this Plan that now has been in effect for 5 years.

So we're going to go through each of these

objectives. And we'd like to listen to perspectives from the various members of this Planning Group about the progress that's been made. And if progress isn't being made adequately, what some of the barriers might be to making progress.

So let's go ahead and start, unless there are any questions from any of you?

Dr. Koroshetz: Yes, it's Walter. I just wanted to make one point to the Group. It’s that as we dealt with the progress in Question 2 aims, in the previous Strategic Plans, we broke it down into a number of different areas.

So I'd like to just repeat those so people will have them fresh in their head, because they're all relevant to the individual objectives we go through. So they were brain imaging, neurophysiology, molecular basis of phenotyping, immune system, and co-occurring conditions.

That's how we had parsed out the progress in these different areas in the past. But I think if we go through each of the nine, I think -- just to keep in your mind -- those are the kind of things

that we had been looking at with that.

Dr. Daniels: Okay. Thank you. So we'll start with Objective 2.S.A., 2 short-term A: "Support at least four research projects to identify mechanisms of fever, metabolic, and/or immune system interactions with the central nervous system that may influence ASD during prenatal-postnatal life by 2010, and fever studies, to be started by 2012."

And in the previous call, the Committee members who were on the call felt that the recommended budget for this objective was met and many projects were funded in this area, but the field is still developing and there's a need for continued emphasis on this.

What do you as members of this Group and experts in the field feel has happened in the past 5 years on this -- in this area of research? And what do you think is continuing to be a need? Or what are maybe the emerging needs in this area as well?

Dr. Pardo-Villamizar: This is Carlos Pardo. I work in immunology. I follow closely research

related with autism immunology, and obviously, fever is one of those issues.

My understanding is this is a very hard topic actually because there are some clues that fever may modify behavior in autism. My understanding at this moment is, actually from the literature, is that we don't understand the mechanism. And at this moment, I don't think that we have too much information.

I don't know necessarily where, which are the studies that were funded for this period. But so far, I don't think that we have moved so far in understanding the mechanism of why fever is modifying behavior in autism.

Dr. Koroshetz: It's not just fever. It's interaction in the immune system in autism and metabolism in autism. So it's broader than just fever.

Dr. Pardo-Villamizar: Right. So in that aspect, I think that probably the most important progress has been on the genetic characterizations of patients with autism in which there is clear evidence that, not necessarily that the genes have

associated with synaptic function of not necessarily on top of the list of genes as associated with autism.

But also, a very good number of genes that are associated with innate immunity that appear to be important. And that probably is the best advance in the past 3 or 4 years. And I think that the work that has been done by Dan Geshwind at UCLA has been probably one of the most important advances for understanding how the immune system may be associated with autism.

The other aspect that probably is important is in some way that progress has been done at the studies at UC Davis by Judy Van de Water, her group, on having a better characterization of the immunological background of these patient populations.

Dr. Koroshetz: Right. And then in the past year also, you know the issues of animal models that have been developed by immune-challenging mothers in the first or second trimester. The role IL6 in inflammation as well as autism, the antibodies that have been discovered in some

mothers. So Carlos, how would you -- do you think -- how do you see those stacking up? Mainly, you know, looking at the maternal immune --

Dr. Pardo-Villamizar: Yes. I think that that is one area in which I believe there is a need for work. I think that the interaction of maternal environment and the genetic background is critical for understanding autism. So I think the animal models will provide at least some partial view.

I don't think it's going to be a definite understanding, but at least a better understanding of how the innate immune system and other elements of the immune system intervene during brain development to make subjects susceptible to autism spectrum disorder.

So I think the models that have been developed, actually, are very interesting. I think that there is a need for pursuing those models.

The other thing that is probably important is there is a growing interest in knowing how maternal infections affect or modify the result for autism, but the potential effect of neurotoxins on immunological settings that

eventually will modify brain development.

So the environment, not only given by infections, but also by potential neurotoxins, and all the elements of maternal environment and interaction with the immune system are probably one of the major focuses that we should have in the future.

Dr. Daniels: Thank you.

Ms. Redwood: I actually wrote that. Walter and Carlos, I also wanting to mention from a parent perspective. And what I hear from other families is that it appears as though the children that have a favorable response to fever, where their autism symptoms actually dissipate during episodes of high fever, those children may be the ones that have better long-term outcomes from what I've heard in talking with parents.

And the other thing that I've heard recently that I think is hugely important was from a parent whose daughter with autism was also diagnosed with leukemia and that when she underwent chemotherapy, evidently, the chemotherapy drugs were a little too aggressive, and they knocked out her immune

system.

During that time, she recovered from her symptoms of autism. When her immune system started to come back online, her autism symptoms started to reappear.

So I think, you know, there are definitely some very strong connections there between the immune system, metabolic, and fever in these children.

Dr. Minshew: Is that going to be a case report, do you think?

Ms. Redwood: I don't know. I mean, I could put you in touch with the mother of the child. I think it would be wonderful to write up.

Dr. Minshew: Well, it would have to be her physician who would write it up -- mother and physician in combination, I guess.

Ms. Redwood: I will reach out to her and ask her about that. I know my son also responded very favorably to fever. And, you know, he's 19 now and in college. So he was one of these children who had a very good outcome. So I think there's something about fever that may help us to predict,

you know, how these children do long term, too.

Ms. Singer: Okay. I mean, but when you're talking out of one, I mean, Jodi also has positive response to fever. She does not have such a happy outcome right now. So you know, I think a lot of these only one anecdote has to be verified by --

Ms. Redwood: Oh, Alison. I agree that trying to parse out some of those responses, I think, are important.

Dr. Pardo-Villamizar: So I think that those are interesting elements. I think that in the future, we need to have a very serious and well-designed clinical epidemiological assessment of the issue of fever, because, unfortunately, with these anecdotal reports, we are not able to build that in terms of mechanism or understanding.

So I think that probably in the future, a multicenter study that approached from clinical epidemiological point of view, they should -- for fever -- need to be taking place. And I think that probably there is a lot of enthusiasm in different centers for more info with that idea.

Dr. Pelphrey: This is Kevin. I want to second

that idea of most epidemiologically based assessments, while it wouldn't be epidemiological samples, everyone -- maybe one of the samples with BH network that would be within the ACE centers would be epidemiological study.

It might be good and very cost-effective to add critical questions about fever and responses to fever into those already funded studies while they're just getting very -- collecting those numbers is subject --

Dr. Koroshetz: So as far as you know, no one is tracking that?

Dr. Pelphrey: Well, I think everyone is asking about it in their own idiosyncratic way. It would probably be a good thing, a case where it would be good, to all be on the same page about how we're asking it, especially the epidemiological study out of Mount Sinai. I'm blanking on the investigator's name right now, but it's a network.

Dr. Pardo-Villamizar: Yeah. I think that there is already a very well-established network of centers with subjects that have a very good and detailed genetic analysis. And I think that those

are the -- that's the – base of a potential population-based study on fever, because those are the reason we already have a lot of understanding of the genetic situation by gland, genes, and other things.

And probably cost-effective to take that population of things already known and do probably a 1- or 2-year follow-up that, in any rate, would detail what is the effect of fever in behavior as well.

Dr. Pelphrey: That's a great idea.

Dr. Koroshetz: Hey so how about -- So the other thing that's on that list is metabolism, metabolic abnormalities in autism. So in my line, that gets us to the mitochondrial side, but there were other areas. Does anybody want to make any comments of what they think we need to move in terms of metabolic defects in autism?

Dr. Minshew: Can I just ask about what people think of the PET study, the microglial activation, if there's been one published?

Dr. Daniels: Who's speaking?

Dr. Minshew: Nancy.

Dr. Daniels: Oh, thanks.

Dr. Koroshetz: Hi, Nancy. Anybody know the name of the study you mentioned?

Dr. Minshew: PET studies of microglial activation in the brain.

Dr. Pardo-Villamizar: This is Carlos Pardo. I do not want to monopolize my interventions here, but that is a very interesting study. I am interested in microglia. I think that the study is following some of our initial report on microglia effective -- active -- in patients with autism.

Unfortunately, microglia, have a lot of normal function and occasionally bad function. The rationale for already microglia is very important. I think that the ligands or the material, the ligands, that we're using in that study were not necessarily state of the art for microglial studies. And I believe that there is a lot of work, including work at the NIMH by Bob Innis, looking for better biomarkers or ligands for microglial activation.

And I think that the future is -- yes, it is very important to understand what is the stage of

activation of microglia in the brain of patients with autism and I think that will provide interesting clues.

A note of caution is, microglia is a normal cell of the brain and not necessarily microglia is doing bad things in the brain. There is a lot of information the past couple of years from animal models that microglia is very critical for synaptic building in the brain.

So I wonder if microglial activation is participating in some sort of modeling process in the brain, not necessarily in bad things. I think that it's important to clarify that because there is a lot of misuse of the term "microglial activation," with the connotation that microglial activation is doing bad things in the brain. And I think that that is a concept that is evolving quickly, and probably we understand now that microglia is actually very helpful and beneficial for synaptic organization and when it functions normally in the brain.

And I think that the PET scanning is going to be interesting, helpful. I think that they need to

use better tools, better ligands to have really reliable identification of the patterns of microglial activation.

[Pause]

Dr. Daniels: Other comments on this one?

Dr. Koroshetz: Does anybody want to talk about -- talk to the metabolism part of this objective? The metabolic defects in autism?

[Pause]

Dr. Daniels: Do you have anything, Walter, on metabolic issues?

Dr. Koroshetz: Well, I think, you know, there's the story of mitochondrial mutation associated with autism. And also attractive is the idea that mitochondrial diseases cause both the system dysfunction, so GI tract seizure is cognition you know, are also -- mitochondrial disorders, as well as what you see in autism.

My sense of it now is that, you know, there are clear -- there are clear -- links. So I think I would be on the group that favors a link between mitochondrial disorders as a cause of a subtype of autism. I don't know that I would be on the -- I'm

anxious to see what people think about whether you know non-syndromical autism is -- if there's evidence that that is a mitochondrial defect there as well. That seems less secure in terms of my reading.

[Pause]

Dr. Minshew: This is Nancy again. Would you say that's related to the oxidative stress that investigators speak about?

Dr. Koroshetz: Yes. The oxidative stress is difficult because, you know, that could be inflammation related. It could be mitochondrial related. Or it could be other confounders. It certainly has been studied in which mitochondrial stressors have been measured.

In terms of the strength of the evidence, where do people stand on those studies, those of oxidative stress being a marker in autism? Is it something people would think of as interesting, not interesting, or already nailed down?

Dr. Pelphrey: This is Kevin. I see it as interesting but nonspecific.

Dr. Pardo-Villamizar: I do agree with that

statement. I think that the topic of mitochondria in autism spectrum disorder is interesting. I think that probably there is a sub-sets of patients with autism that may have some mitochondrial disorders.

The problem is, at this moment, we don't understand what is the prevalence of mitochondrial disorders in the general population, because there are some mutations that express clearly with neurological abnormalities, but there are also self-mutations, some mitochondrial genes that are basically not manifested or manifested only when there is a stressor.

I think that, for example, the best example is this young lady who had a vaccine and later developed the symptomotology of autism and was found later with a mitochondrial disorder. So that's a disorder of the sort in which there is always the concern about autism.

How big is the tip of the iceberg? I think this is still very small. But I think that the whole genomic analysis in the future may give a clue, from the genetic point of view, is how

prevalent those mitochondrial mutations are present in the autism population. And that clearly will be a different window.

I think that the window for assessment of oxidative stress, unfortunately, is extremely influenced by several factors, including inflammation. It's going to be very difficult to dissect clearly what is the role of oxidative stress mitochondria in patients with autism.

Dr. Minshew: This is Nancy, again. I've seen a couple of these proposals. And it seems as though the -- it's not clear how to move it ahead in terms of the methodology or the approach. And I think if we could gather up the people that really understand these issues and craft a statement of need and direction, even if it's just development of some methods, that that might help. The same thing I think would apply to immune issues.

Dr. Koroshetz: I think kind of a standardized approach to that could be used across multi-centers to get at these questions.

Dr. Minshew: But that's -- yeah. That's not exactly what I was thinking. I think that there's

not quite enough guidance when there's a call for proposals in this. There's not quite enough guidance about what the specific questions are that need to be answered and a range of ways that they might be answered.

Dr. Pardo-Villamizar: Like a workshop type of meeting that establishes or outlines how it's going to be the methodology for evaluating of oxidative stress mitochondria in autism? Is that what you mean, Nancy?

Dr. Minshew: I think that might help. You know, the few proposals that I've seen would have one area where they -- were -- seemed to have a good grasp of things but other areas where they just didn't have a grasp. And s, I think there are some groups that are interested in this that may make some inroads.

But I think that it would be very helpful to have the relevant experts in a room to talk about the evidence that exists, what could it mean, what could it not mean, and multiple possibilities. It's like microglial activation -- it may not be a bad thing. It may be constructively shaping

dendritic morphology.

So that anybody who puts in a proposal in this area at least considers what is known and what methods might be applied to advance the field. Otherwise, a proposal goes through a review committee, and you may or may not have a person on that committee that is expert in, say, mitochondrial dysfunction. You know what I mean?

Dr. Pardo-Villamizar: Yeah. In Autism Speaks, I believe, they gathered a group of people with interest in mitochondrial disorders a few years ago. I participated in a meeting 5 years ago on immunity and autism for Cure Autism Now. So I feel like there have been some attempts to outline those guidelines.

Unfortunately, the field of mitochondria and field of immunology is evolving so quickly that actually the conclusion of some of those [Inaudible comment] are already outdated. So I think it's a very interesting topic for a workshop to establish some guidelines for future assessment of immunological function, for example, or mitochondrial oxidative stress function.

I'm sure that there is a lot of interest around the country about those topics.

Dr. Daniels: Great. Well, it sounds like we've had a pretty robust discussion on this first objective. We have another eight to go through.

Are there any other comments on this one before we move on?

Ms. Redwood: I would just suggest that if we move forward with a workshop, which I think is a great idea to bring some of the experts together, to include clinicians who are actively screening children for mitochondrial disorders and that they be involved, too.

Because, from my understanding, they are seeing quite a bit of mitochondrial dysfunction that wouldn't be labeled a true mitochondrial disorder. And they're not really finding a genetic reason for what's causing the mitochondrial dysfunctions. So I think it would be important to bring those folks to the table, too.

Dr. Daniels: I think that the Group isn't in a position to actually, you know, propose a workshop per se. But when we go to the meeting next Friday,

if that's something that becomes a Committee goal that they would like to try to put forward in some way, they can do that.

Go ahead. Is there another comment on this one before we move on?

Okay. Let's move on to the next one. 2.S.B: "Launch three studies that specifically focus on the neurodevelopment of females with ASD, spanning basic to clinical research on sex differences by 2011."

And on this one, the Group last time determined that the recommended budget for this objective was partially met, and more than three studies were launched but that further work is needed in this area.

Noting that there's an ACE that is focusing on this area as well.

Dr. Koroshetz: So is anybody aware of any major findings that have come out so far in terms of female/male differences in development in autism?

Dr. Pelphrey: This is Kevin. The biggest news is right now out of -- our ACE -- is the

differences in genetic, the differences in how copy variations sort of work to cause autism in boys and girls, and then the major protective factor of being a girl, requiring a greater hit in terms of the number and size of copy-number variations.

And so some of that work is out now and published out of – Mike Gugliar's group is not involved with us. And now out of [Inaudible comment] group with Stephan Sanders, publishing on that, and that's to appear shortly.

And then, otherwise, there's just a steady stream of findings about brain differences and brain development differences. But we won't be in a position for a couple of more years to have our sample sizes large enough to publish anything definitive on brain differences.

Ms. Singer: I would add that there's also emerging work on treatment response differences in males and females. When typical response treatment and [Inaudible comment] different school-based interventions. And that these are noted clinically in the community and on [Inaudible comment]

Dr. Pelphrey: That's right. There's going to be -- I think that this relates to one of the other questions about individualized medicine and charting developmental trajectories in order to understand individual differences and therefore make treatments that are specific.

I think, you know, something that really needs to be focused on is using genetics and brain imaging to understand treatment response differences in boys and girls, to behavioral treatments that are already empirically supported, but typically they are only empirically supported at the level of very small studies, and then mostly in boys.

Dr. Koroshetz: Any other comments on this one?

Ms. Singer: Well, I thought the other interesting thing that I saw presented at the Simons Foundation conference had to do with the idea of females who had the genetic hits but did not express the clinical phenotype. And they started tripping on this concept of "carrier moms," that there were siblings and there were moms that had the genetic -- and that this may

lead us to an understanding of a potential protective factor.

You know, what is it that prevents these girls from -- who have the genetic hit -- from expressing the clinical phenotype?

Dr. Pelphrey: Yes, that's a good point, Alison. And it also highlights that knowledge being able to inform the design of novel individualized treatments that target bringing about those compensatory and protective factors as opposed to directly trying to normalize aspects of abnormal brain development.

Ms. Singer: And it gets toward aspects of prevention, which I think are really important to talk more about.

Dr. Pelphrey: Yep. Absolutely. Early identification and prevention.

Dr. Daniels: Great, any other comments on this one? Okay. Let's move to 2.S.C: “Identify ways to increase awareness among the autism spectrum community of the potential value of brain and tissue donation to further basic research by 2011.”

And in the call that occurred this morning on Question 7, we talked a little bit about this. This Group last time talked about this as well. And we've provided a short summary that the recommended budget for this objective has been partially met. And in 2013 that NIH launched the NIH neurobiobanks for $5 million, which include samples for research on autism as well as other brain disorders. And that those dollars are not reflected here because they're not autism specific.

And in particular, that the NIH neurobiobank has a Web publication, *Live Brain Donation: A Legacy of Hope*, that addresses this in particular, the value of brain donation. And Alison, on a previous call, talked a little bit about this and some of the private efforts that are ongoing and efforts for increasing brain donation.

So Alison, do you want to mention those here?

Ms. Singer: Yes. So I'm a little bit concerned about the way this is presented on this page. I think a lot of what's included in that $850,000 is not for awareness. It's really having to do with -

- you do write here that it has to do with -- tissue processing.

But tissue processing is not part of the objective. So I don't think it should be included.

Also the -- you know, I've looked at the *Live Brain Donation: A Legacy of Hope* publication when we were putting together our coming campaign. And that publication mentions several diseases, but not autism. So you know, I think it's misleading to include that here as an autism awareness publication, when it's really a missed opportunity to talk about autism brain donation.

That said, after having this objective appear in the Strategic Plan since 2009, there finally now is a specific project being funded by the Simons Foundation that is specific to increasing awareness of the need for tissue donation. It's being launched in conjunction with a coordinated brainbank that's being overseen by David Amaral. That will have four nodes: one at the MIND Institute, one in Texas, one in Boston, and one at Mount Sinai.

And that brainbank will coordinate collection

of tissue, processing of tissue, and dissemination of tissue. And with that, there will be this coordinated outreach and awareness program toward families and other stakeholders in the autism community -- and in the broader community -- that speaks specifically to the need for donation of autism tissue and control tissue.

So I think in 2013, we finally have the real first project towards 2.S.C. But, you know, I think it's a little overstated the way it currently is written.

Dr. Daniels: So Walter, you might be able to speak to this a little bit better. In talking with the NIH people who are working on this, my understanding is that NIH's philosophy is to approach this by doing a shared effort that targets many diseases at the same time and that they weren't likely to launch an autism-specific initiative for this. And so this initiative is meant to cover autism as well as other things.

So I think they felt that it should be acknowledged. But certainly, the information that you shared today should also be included about the

autism-specific brainbanking initiative.

Ms. Singer: I think just some feedback for the group that's running that at NIH, is they mentioned many diseases, but they don't include autism. It would be great if they could add autism.

Dr. Daniels: I guess I wasn't aware that autism wasn't included.

Ms. Singer: No, they talk about -- I remember they talked about Alzheimer's, they talked about Huntington's, they talked about Parkinson's, and how all of those disorders are in grave need of brain tissue. But they don't talk about autism. I would love to update those materials to include autism.

Dr. Pelphrey: This is Kevin. It would be great to sort of put it at the beginning and the end of all their materials in terms of the advertising approach, so that it really stands out.

Dr. Pardo-Villamizar: This is Carlos Pardo. I think that I Alison’s statement is very well received. I think that there is an extreme need to get brain tissues. And I think that everybody

needs to be working on these issues, from clinicians involved with patient care, to researchers. Because that is -- I mean -- we are getting a lot of mileage in neuroimaging. We are getting a lot of mileage in genetic studies.

To tell you the truth, the only way to deal and understand a brain function requires taking a look at the brain and the cells in the brain. So this is urgent need to collect more brains.

At this moment, there are no necessarily -- the brain by the ATP's is not necessarily a collecting a good number of new cases. And if you take the statistics that they have; I mean, there are no more than 10 new good cases for studies every year. And I think that there is a need for emphasis on this issue.

Dr. Daniels: And Question 7 did talk more about brainbanking itself. And this particular objective is more about awareness.

Ms. Redwood: There's also been activities through the Eunice Kennedy Shriver NICHD Brain and Tissue Bank with the University of Maryland to increase awareness and to promote, you know,

donations for both donor and ASD. I know they've been going to different conferences -- they've been very involved.

I don't know what their actual numbers are now, but I think it would be nice to support the work that they're trying to do, too, to increase brain tissue donation.

Dr. Daniels: Walter, do you have any comments about the NIH efforts at all?

Dr. Koroshetz: Yeah. Well, I think it's a work in progress. It's just being set up. The operational goal is that you have a system that is finely tuned and that can be disease nonspecific at its base but that it can take in projects that are disease specific. So we are planning a dramatic brain injury initiative where we're relying on the NIH brainbank to bring in, donate -- some people die of their head injuries.

I would think that same mechanism is also true of autism. And I think it's a matter of adding on the disease-specific outreach to take advantage of the scheme that the NIH is setting up.

I guess one other thing, I guess is that we

have to be sensitive to is that whatever the ACE is doing and what the Science Foundation is doing is coordinating. We'd want to ask, you know, dual messages or, you know, it's actually a bad thing. It's very sensitive especially with families about brain donations. You want to have a unified method.

Dr. Daniels: So we can try to get in touch with the NIH people who are working on the NIH neurobiobank. And they had given us the impression that autism was included here, and that's why they provided the information. But if autism is not --

[Inaudible comments]

Dr. Daniels: -- comments of the Committee. Sorry, what?

Dr. Koroshetz: It's definitely included; no question there. The issue is how the outreach is going to be done. Because that's got to be, you know, targeted toward diseases. So we may need to add that piece as the contracts come up.

Dr. Daniels: Okay. Yes, my understanding was that autism brains were a part of it.

Dr. Koroshetz: Yes, that's true.

Dr. Pardo-Villamizar: One of the limitations of the brainbanks at this moment is not only collection of diseased brains, but actually -- fortunately, not too many of our kids, normal kids die -- but also, there is a need to establish a collection of normal brains. And I think that that probably, with NIH or entities effort to the offices of medical examiners around the country to encourage the participation of brain donation, normal brain donation, I think is needed.

Dr. Daniels: I think that is part of Question 7, but we can note it.

Ms. Redwood: Susan, can you also reach out to the NICHD Brain and Tissue Bank? I think Ron Zielke is the person who's heading that up. And find out about their specific initiative. I know they have a program on autism. They have autism-specific endeavor and autism-specific outreach.

So if we're talking about planning to coordinate it would be good to have their information included.

Dr. Koroshetz: So Lyn, they, we there are actually moving all of the NICHD, NINDS, NIMH all

into one brainbank system. So that's definitely -- that's coordinated.

Ms. Redwood: All right. Very good.

Dr. Koroshetz: Yeah.

Dr. Daniels: All right. That's why we didn't do that separately.

So let's move on to the next one, 2.S.D: "Launch three studies that target improved understanding of the underlying biological pathways of genetic conditions related to autism, such as fragile X, Rett, tuberous sclerosis, and how these conditions inform risk assessment and individualized intervention by 2012."

The Group last time thought that the budget recommendation had been met and that there were a large number of projects funded that address this objective, and, you know, that there's been quite a bit of growth.

There's an ACE center that's focused on tuberous sclerosis. And the objective in general is on track. But we want to hear from you about, in terms of research, what are the challenges in this area? What are the areas that might be, you

know, not as well addressed as they could be here? Are there any barriers?

[Pause]

Dr. Koroshetz: I was thinking, you know, from the biology point of view, these are the -- this is the one that probably seems to have progressed the most over the last 5 years. An amount of information is coming out now from these monogenic, highly penetrant disorders, has led to identification of pathways that, you know, look like they could be causally linked to the disease.

The proof is always in, you know, whether you can make an intervention to improve things. And that -- you know, like many other neurological diseases -- that's a tough road to go. But that's what we're doing, you know, so Parkinsons, epilpsey, you know, we have these targets. Same now with fragile X, Rett, and TSC, I guess.

So I think there's been a lot of progress here. You know, it's certainly not to the point where it's a therapy. But there are a lot of leads to go after.

In terms of how it informs the nonsydromic

autism, I think that's a little bit trickier. There certainly are, again, overlaps from the [Inaudible comment] studies that indicate that some of the things from Rett, for instance, and fragile X, may be important in other persons with autism. But that's a little bit more difficult to nail down.

So that's how I see this now, with lots of progress, particularly in these individual disorders. Generalization is still something to -- needs a lot of work. Any other people see this area differently?

Dr. Pardo-Villamizar: I feel that's a fair assessment.

Dr. Pelphrey: I agree with that.

Ms. Singer: I think that was very well said.

Dr. Daniels: Good. It sounds like you're in agreement about that one.

So let's move on to 2.S.E: "Launch three studies that target the underlying biological mechanisms of co-occurring conditions with autism, including seizures/epilepsy, sleep disorders, wandering and elopement behavior, and familial

autoimmune disorders, by 2012."

The Group last time felt that the recommended budget had been met for this objective and more than 20 projects were funded but that further efforts were needed, especially on wandering, metabolic and immune conditions related to ASD, as well as a systems biology approach to understand how these co-occurring conditions are related to ASD.

What are your thoughts about how the field is progressing in this area? And what are the remaining needs or continuing needs?

Dr. Pelphrey: This is Kevin. Backing up a little bit, as I read that paragraph, it seems so broad that it's almost impossible to miss. Having a large amount of work in the area, it sort of -- it lumps sleep issues and wandering and elopement all in the same kind of thing. And the different things that it mentions would be tackled in many different ways using many different methods.

And so I'm worried that that needs to be dissected out a little bit so that we can get a better sense of how we're targeting things that

have -- that fall in the different areas. You know, say, wandering and elopement are something that we could do something about rapidly, increase awareness and other methods, whereas, you know, understanding sleep disorders would be a whole different ball game.

And they would have different timeframes for impact.

In comparison to the rest of our goals, we've got one that seems a bit like a catchall. That said, it's also about those things which co-occur with autism, and of course, that's many, many things. I don't know if there's anything we can do about it. But I'm suggesting you might want to think about it.

Dr. Koroshetz: Yeah, good point. So Kevin, if you'd just try and dissect it down, I would say -- you know, what do we know about the biological mechanisms of wandering and elopement in autism. I don't know that we know anything.

Dr. Pelphrey: Right. Yeah. We know nothing, and it's something that really needs to be looked at.

Dr. Koroshetz: That's right. We don't know anything. It's no problem. In terms of seizures, we know -- I guess the only thing I could say is that we know -- something about the mechanism underlying seizure activity. We know something about, at the synapse level, you know, there are some clues that there are synaptic dysfunctions. Maybe that gets you to seizures as well as autism. I don't know anything more concrete than that.

There are some studies that John picked up in terms of the models -- autism models -- including immune activation in pregnant mice that show that that actually changed seizure thresholds as well as gave autistic behaviors. There's a story of IL6 in that model and IL1 giving rise to epileptic form activity and IL6 related to autism-like behaviors.

Those are the kinds of things we came up with, tying epilepsy and autism together. I guess a lot of genetic, CMV mutations, copying variance; they frequently have epilepsy and autism as tied together. Anybody else in terms of mechanisms, tying autism and epilepsy together? Know of any

other areas that look promising?

Dr. Pardo-Villamizar: I mean, taking a look at autism and neurological disorder, I mean, despite that all the majority of studies show that there is some disarrangement of neurological organization in the majority of the patients, obviously, that is the setting or the right setting for the development of seizures and epilepsy.

So, I mean, I view this mostly as comorbidity in the setting of autism. So I mean, these patients are obviously going to have high risk of seizure disorders because of the cortical abnormalities as well as the sleep disorders because the disturbance in the pathway organization.

There are area which obviously -- we don't have a good understanding like of wandering and elopement behaviors. So I feel that it's a little bit of a mix of different things here. I feel I agree with Kevin in the initial statements. So…

Dr. Daniels: What about the familial autoimmune disorders? What do you think is the

status of that area?

Dr. Pardo-Villamizar: Well, there have been early studies in the past few years about the familial autoimmune disorders. Again, this is an issue in which the best approach is doing a very well-designed epidemiological characterization. Unfortunately, many of these studies on familial autoimmune disorders came from a series of cohorts that are obviously biased.

I think in the future, probably, in the same way that we mentioned about the age of the immunity and fever, I think that different centers that have accumulated in large populations should get the effort together to have a characterization of familial autoimmune disorders.

And I feel that that's not difficult because, again, if they have a group, they have clinical epidemiological design, they can catch and they can do an assessment. Autoimmunity needs to be defined clearly. I mean, almost 25 percent of the population of the United States may suffer autoimmune disorders, from the skin autoimmune disorders to thyroid skin disorders. So there is

still a lot of noise in the background of autoimmunity and what is the meaning of autoimmunity.

So again, a well-designed study that captures the information that many centers have already accumulated probably will be the best approach to clarify that issue.

Dr. Minshew: This is Nancy. Is it possible to move the familial autoimmune disorders up to the section that talks about immune alterations in autism?

Dr. Pardo-Villamizar: I feel that is a fair approach. I think that, yeah, that will decontaminate a little bit, if I can use the word decontaminate it. It will contaminate a little bit this aim here and move up to immunity? Yeah.

Dr. Pelphrey: This is Kevin. I think that's a great idea.

Dr. Minshew: It's Nancy again. The other question I had is, when they're doing these epidemiologic studies, they're relying on a parent's report of the diagnosis, without necessarily ever having direct documentation of

the diagnosis.

Another possibility is to go directly perhaps to autoimmune clinics, where you have confidence that that diagnosis is solid, and looking at the babies that these women have. I don't know if that would be an acceptable alternative. But we've done a number of the other kinds of studies, and I don't know how much clearer it's going to get.

Dr. Daniels: So in terms of actually changing language in the Strategic Plan, that's something that would be up to the Committee whether they would do that. But we can note that the Planning Group felt that there was some confusion by adding autoimmune into this particular objective.

Dr. Koroshetz: How about the sleep? Anybody else have any thoughts about the sleeps or sleep studies? You know, melatonin abnormalities and Flexazone and circadian rhythm abnormalities?

[Pause]

Is there a consensus in the community about what the abnormality is and whether or not there's a biological basis for the abnormality that, you know, could be a hallmark of autism? Does it go

back that far off?

Dr. Minshew: Well, this is Nancy. I think there are two issues. The first is the general category, clinically, of kids with therapy having sleep problems. And then they would also be extending them to adulthood. And that has a broad range of potential contribution.

The other side of it is that we've seen that there are mice models, genetic models, where alterations in circadian rhythm are part of the expression of that genetic alteration. But I don't know that we've necessarily melded those two together in ASD.

Dr. Daniels: Well, it sounds like, overall, what I'm hearing the Group saying -- and you can correct me if I'm wrong -- that it sounds like work has started in all of these areas and many projects have been launched, but there's really no depth of knowledge at this point about any of these co-occurring conditions and that much more research is needed to create a stronger understanding of the biological mechanism behind these co-occurring disorders.

Dr. Minshew: Yeah. I think the ATN sites have done quite a bit on sleep itself in terms of trying to help parents with ways of promoting sleep. It would be interesting to see what they thought about the underlying causes of the sleep problems. You know what I mean?

Dr. Daniels: Um-hmm.

Dr. Minshew: Poor sleep, basically poor sleep hygiene and kids, if they do it once one way, they keep doing it that way.

And how many of those kids did they think it's really a circadian rhythm issue?

Dr. Daniels: We should have someone from ATN at the meeting next Friday. So that's something that could be brought up there.

Dr. Koroshetz: Do people use melatonin to treat kids? What's the feeling? What's the evidence behind that?

Ms. Singer: With regard to sleep?

Dr. Koroshetz: Yeah. To treat sleep disorders in autism?

Ms. Singer: There were some studies of melatonin that came out -- I think, last year or

the year before -- that were presented at IMFAR.

Dr. Koroshetz: Um-hmm.

Ms. Singer: We should get some input from Beth Malow.

Dr. Koroshetz: Okay.

Ms. Singer: She's really is sort of the go-to person on sleep.

Dr. Koroshetz: Right. We had Beth on our Group last time. Yeah, she's a good friend – I'll let you know…

Ms. Redwood: Walter, just a quick question. Going back to looking at the underlying mechanism, especially with regard to epilepsy, there are some articles in the literature linking like, neuro-inflammation and epilepsy, especially in the pediatric population.

I want throw this out as potential sort of mechanism that might underlie, you know, the seizure activity in ASD. And I don't know if there's been a lot of research in that area. But it would be, you know, a potential new target for treatment for seizures.

Dr. Koroshetz: Right.

Ms. Redwood: You know, a lot of kids with ASD have intractable seizures, and they're very difficult to control with the standard seizure medication.

Dr. Koroshetz: Right, I --

Ms. Singer: You could make that query about sleep as well. I mean, I think the studies that have come out about sleep have focused on trying to fix the sleep problems with intervention. But they don't really get yet at the underlying causes of sleep, except what we've seen just from the -- I guess the -- epidemiological studies.

It's that for most of the kids, it's not an issue of sleep onset and so the issue of hygiene may not play as much of a role as sustaining sleep. Many of them fall asleep at the same time each night, as they should. But then they wake up in 3 hours. And they seem to just need very little sleep.

And so I don't know that we've really gotten to the underlying cause of that, that that's been as much studied as some of the issues of how to prevent it.

Dr. Phelphrey: I think --

Ms. Redwood: Alison, I think there were reports too, in terms of abnormal GI problems, like reflux, that could very well be causing a lot of the sleep abnormalities. And when those underlying medical problems are treated, the parents were reporting better sleep in their children. But, again, it needs more research.

Dr. Pardo-Villamizar: This is Carlos Pardo. I'd like to make a comment about the issue of epilepsy and inflammation. It is right. There is a lot of interest about the role of inflammation in pediatric epilepsy right now. However, again, a note of caution is the immune system reacts any time there is a disruption of normal function. And it seems to happen in any type of neurological condition. It has happened in autism and epilepsy; the innate immune system is active.

So that doesn't mean that that's the cause of the problem and is probably a secondary reaction to what is going on in the organ. And it's basically what we call a mechanism for homeostasis -- try to maintain the normal situation in the

brain. However, I agree. I think that there is a need to understand if that, by ground of epilepsy in patients without [Inaudible comment] has by its own sort of disruption of the innate immunity.

I caution about treating inflammation in epilepsy and autism, because I don't think that this is the right approach. We need to understand first the mechanism before we commit to issues of treatment.

Ms. Redwood: Right.

Dr. Koroshetz: Right. So at NIH, they look at that microglial marker that was mentioned earlier in people with epilepsy. We can see it in the brain. This is not people with autism, but people who have seizures. And it's not clear, as Carlos mentioned, whether the microglial is there for a good reason, to kind of prune the synapses down as a compensatory mechanism to the epilepsy or whether they're contributing.

Ms. Redwood: Right.

Dr. Koroshetz: So it's complicated.

Ms. Redwood: But we need research to better understand that.

Dr. Koroshetz: Yes. Yes.

Dr. Daniels: Are we ready to move on to the next?

Let's go on to the next one, 2.S.F: "Launch two studies that focus on prospective characterization of children with reported regression to investigate potential risk factors by 2012."

And the last time the Group met, they felt that the objective had been partially met, that there were some projects in this area, but that further work was needed to compare regressive autism to non-regressive autism and that it might be useful to take advantage of high-risk siblings as a population to do a study.

So any other thoughts about this, about what needs to happen to move this area forward? And what's the status?

Dr. Pardo-Villamizar: Carlos Pardo again. I am not able to talk for Sue Swedo, but I think that the studies at NIMH are very well focused on the characterization of regression. And I think that among clinicians working with this issue, there is

now somewhat of a consensus that the dichotomy of regression and non-regression is not a dichotomy, but that it's part of a continuum.

So I think early in the future, there is a need of understanding what is the conclusion of all of those studies having been carried out by these groups? The conclusion is it doesn't look like the regression is a different form of autism.

Dr. Minshew: Yeah, this is Nancy. I think it would be very helpful if they went ahead and were able to publish their experience, the internal intramural NIH autism research.

Dr. Pelphrey: This is Kevin. Just echoing Nancy's comment, I think the field is sort of coming to a consensus that regression and non-regressive kinds of autism are a continuum. But I don't know that we're coming to that consensus on the basis of empirical data.

The imaging studies that have been done by people like Nancy and myself have focused primarily on fairly high-functioning, usually not these sort of catastrophic, regressive cases, certainly not late regressive cases. And I think

the jury is still very much out.

You know, we have unpublished findings. You know, I was working on them before the call trying to get them to the point of being ready for publication, that regressive autism in imaging, especially when accompanied with low IQ, which catastrophic regression usually is, is very different in brain phenotypes than high-functioning autism that we've all studied for years, and surprisingly so.

So not something I hypothesized or would have thought. But in many cases, a lot of the common findings from the high-functioning kids don't hold in these kids. And so I don't think the data is there to say that this is or is not a different kind of autism. And I think that if the data that, you know, we're seeing -- and Helen in her ACE are also scanning these low-functioning kids -- they will have a significant number of regressive cases. I think that we're about to be surprised.

And so you know, I don't want to close the door on it and act like there's consensus.

Dr. Minshew: Well…

Dr. Pelphrey: Yeah, and even the initial infant sibling studies, like Ami Klin's study that this came out in nature, and Joe Piven's brain study on the diffusion tensor imaging, all suggesting that early regressive processes are very interesting and can be captured.

That's pointing toward regression playing a prominent role in all kinds of autism. But there are different kinds of regression in different points in time, which will, I think, ultimately help us understand the heterogeneity in the brain and the behavioral phenotypes and link on to genetic heterogeneity as well.

So I think that we don't want to define it out of existence, to just say, "Oh, well" -- define it out of study to say, "Well, that's just a common part of autism." When it happens and why it happens, I think, are going to be really interesting.

Dr. Minshew: But I think, though, reiterating that, though, Kevin, we probably have a lot of evidence that's being collected already on these high-risk infants that we'll see. So I don't think

the question is being ignored at all.

Dr. Pelphrey: Yeah.

Dr. Minshew: It’s just a matter of getting enough that are in the -- as you say, it's a continuum.

Dr. Pelphrey: Yeah. Yeah.

Dr. Minshew: So the message to bring in, we have to have a large enough sample to say what do they look like? And then what I would want to know is, do they look any different early or later than those who are severely affected by autism, but don't present with the regression?

Once again, I think that evidence is coming. So it's not an issue that's being ignored at all.

Dr. Pelphrey: Yeah, that's fair enough. And so just pushing people to get the things they have out there and to get some consensus.

Yeah, when I'm speaking up I'm speaking up because if we begin to sort of define this out of existence, you know, like the newer *DSM-5* now, you know, childhood disintegrative disorder is no longer recognized, then we lose interest in studies of it. You know, it's hard to encourage a

young scientist to focus on a disorder that no longer exists by virtue of being defined out of existence, when the data, I think, are coming through that suggest it actually is a separate entity.

Dr. Minshew: Yeah. And not to beat the dead horse that is really dead, but as a neurologist, I'd say that childhood disintegrative category was always sort of dirty – and that --

Dr. Pelphrey: Yeah.

Dr. Minshew: -- in that it would show up on the neurologic side as known or yet to be defined degenerative brain disease of children.

Dr. Pelphrey: Right. Exactly.

Dr. Minshew: As opposed to a version of autism?

Dr. Pelphrey: Right.

Dr. Minshew: Like all the other cases of autism?

Dr. Pelphrey: Yep.

Dr. Minshew: So…

Dr. Daniels: Any other thoughts about this area?

Dr. Koroshetz: It sounds like it is important and unsettled, and evidence is people are working on it and it should not be ignored, that it could be very important.

Dr. Minshew: This is Nancy. The last thing that I think is an important issue here is what the scientific community knows about these issues may not even be broadly known within the autism science community, which is one issue.

But the other is what gets out to the public, the parents and those who are not parents of a child with ASD, is kind of minimal. So that we may know a lot, but that doesn't mean the parents or the public know.

And it raises the issue of, how do we better communicate to the public about the state of science? Otherwise, they feel like we're ignoring the issue when we're really not.

Dr. Koroshetz: Well, I think that's what the IACC does. I mean, that's actually one of our big goals. So I think that is a chance to actually put that down on paper in the report.

Dr. Daniels: Definitely. And we can always

have a discussion about regression at a future IACC meeting.

So let's move on to 2.S.G: "Support five studies that associate specific genotypes with functional or structural phenotypes, including behavioral and medical phenotypes -- nonverbal individuals with ASD and those with cognitive impairments -- by 2015."

The Group last time felt that the recommended budget for this objective had been met and that there were many projects funded in the area and that the objective appeared, in general, to be on track in terms of funding.

But what do you feel is happening in the field here? And any areas that need to be further worked on, or not just worked on, but emphasized, particular needs or barriers?

[Pause]

Dr. Koroshetz: What Kevin was trying to get at before, right, about having -- trying -- to use the genetics and the imaging to define particular subgroups, and particularly with regard to how they respond.

[Pause]

Dr. Pelphrey: Yeah. This is Kevin. That's what I was getting at.

Dr. Minshew: I think the other issue that I see is that whether or not this can be approached at a single site that might have 50 or 75 people with the imaging and genetics, or whether these studies should only be done by large consortiums that will have hundreds.

And that's been sort of an ongoing debate locally, is what do you do if you have just the 75 participants in genotyping? Are you -- is that -- can we make that useful and pool it all together, or do we just let this issue be addressed at a network level?

[Pause]

Dr. Koroshetz: You're talking about dissecting populations down into small groups based on the genetics or the imaging structural phenotypes. And you're pretty much saying that you need a multicenter approach. That's how I'd see it.

Dr. Pardo-Villamizar: I agree with that. I think that the future of that clinical [Inaudible

comment] of phenotypic [Inaudible comment] is a multicenter study that really accumulates experience of hundreds and hundreds of patients, rather than few small groups of 75 to 100.

You know the need to get all people involved in this clinical research, understand the spirit of collaboration, is the only way to understand this.

Ms. Singer: I think there were also really interesting work presented on this, again at Simons, that looked at sort of the dose dependence in copy-number variations in that the stronger the hit, the more you could actually see it structurally in terms of changes in cortical surface, in cortical sickness.

And I think that was, for me, the first time that I really heard anything about dose dependence on some of these genetic hits. And I thought that was new.

Ms. Redwood: So when I look at the table, what you have is over 40 studies funded, which suggests to me that you may be at the point where you need to encourage a multisite collaboration to look at

this so you get a large pool sample.

Dr. Koroshetz: I mean, a lot of these also might be, you know, Susan -- correct me if I'm wrong -- but they might be fragile X, you know, looking at phenotypes and that particular group, or Rett.

Dr. Daniels: If they were fragile X or Rett, they would have been in that other objective. Because for the coding, anything that looked at those syndromic forms went into S.D., for the most part.

Dr. Koroshetz: Okay.

Dr. Daniels: So good.

Let's move on to the next one: "Complete a large-scale, multidisciplinary, collaborative project that longitudinally and comprehensively examines how the biological, clinical, and developmental profiles of individuals, with a special emphasis on females, youths, and adults with ASD, change over time as compared to typically developing people by 2020."

And on this one, the Group felt that the recommended budget was partially met and that

several projects have been funded in the area, but that more clinical studies are needed over a longer trajectory to identify issues faced by people during the aging process and to take account of risk factors for other medical conditions.

Any thoughts about this and where the science is with this? And what are the needs in the field or anything that hasn't gotten as much attention as it should?

Dr. Pelphrey: This is Kevin. I think that that's still an apt description of where the field is, especially with regard to wanting to have some focus on the aging process. And there are a lot of studies of adults with autism, but they need to be focused on issues that are of concern to adults, uniquely, you know, transition points and inflection points in development. And so we still need those. I don't think we've really had them.

[Pause]

Dr. Koroshetz: Yeah, I was thinking in terms of that. This study that came out about the eye tracking really seemed to show the power and the

need for longitudinal studies. For those in early developmental stage, but I think, you know, that looked fairly exciting as a longitudinal study that could have big impact. What do most people think?

[Pause]

It almost seemed like it could be diagnostic if it could be reproduced in a larger group.

Ms. Singer: Well, I think, you know, when we wrote this objective, the key word here was really "longitudinal." And when we talked about it, we did talk about looking at longitudinal studies for their predictive value and for their sort of backing into the diagnostic value.

I think the study that you just mentioned is a really good example of why we need these -- why we need more longitudinal studies. I'm not convinced that all of the studies that are counted in this number here are longitudinal. I think a lot of them sort of got in under "comprehensive." But I think the key word here really was meant to be "longitudinal."

[Inaudible comments]

Dr. Minshew: Go ahead, Kev.

Dr. Pelphrey: No, you go ahead, Nancy.

Dr. Minshew: What I was going to say is that the study that was published about gaze in infants is a great example of an age or developmental-level phenomenon that can be very helpful for diagnosis.

But I think likewise there are issues that you implied, Kevin, that transition from childhood to adolescence and then adolescence to adulthood, that have their own unique kinds of questions, you know. So what children --

Dr. Pelphrey: Yeah. I agree.

Dr. Minshew: Yeah. We know that children can go worse, better, or unchanged through adolescence, but we don't understand it very much. And then for adults, which ones make the transition and become competent, which is not a lot? And what happens to the rest, and why is it happening? And what are the mechanisms, and what could we do about it?

So I think the older ages are very neglected in this regard compared to infants.

Ms. Redwood: I agree, Nancy. And that's going to be so critical because so many of the children now are aging. They're aging out of the system. And we really don't know what their health care needs are going to be over time or even their other needs for employment and housing. And that's going to be key to be able to predict, you know, what the children are going to need as adults.

And we really don't have a lot of information about that right now. So it's even becoming more, more critical of a question.

Dr. Pelphrey: This is Kevin. I wanted to second both of those comments. And we have to -- I think we've really done a lot of work on the infant period and particularly on infant siblings. What we have to remember is, to the extent that findings like the new eye-tracking finding are diagnostic, they're diagnostic for infants that we already know are at much increased risk.

It's not a population diagnostic measure, and if we want to develop something like that, it has to work on unselective samples. So you know, any child that walks into the clinic, as opposed to

those that we already have reason to believe are at increased risk.

And so, as was said, an appreciation of those findings in that context, the power of the longitudinal design to predict outcome and response to treatment, beyond the infant sibling years, but into these different transition points, that underlying principle, as Alison pointed out, I think is what we want to capture in this goal, and the excitement of that.

Dr. Koroshetz: Yes. I agree.

Ms. Redwood: And also, this project, you know, when you look at the budget that we have for this and how much has been spent so far, I know it's a long-term project over 12 years. But you know, one of the concerns we have on Question 3 is that it seems as though the funding from initially in 2008 to 2012, a lot of these long-term projects were actually dropping off.

You know, like the EARLI study. And so you know, I didn't go back and look at this one in terms of what projects we have ongoing -- if that funding has been level or if it's been declining

or increasing.

I'll look at that real quick. But that was another concern that we identified previously on another question that may affect this objective, too.

Dr. Minshew: I'm sorry. What is the question?

Dr. Daniels: The question, I think, was whether the funding levels have dropped off on this objective. And if you look in the Cumulative Funding Table, you see that in the first year -- well, it was the year before the Strategic Plan started -- there were 49 projects coded to this objective. [Inaudible comment] any fewer objectives in the Strategic Plan. And that's probably one reason that there were so many projects coded here. And since then, it's varied between 5 and 10 projects. So it hasn't been a very dramatic change; it's always been fairly low.

Ms. Redwood: Right. I'm just concerned about, you know, the need for these large-scale, multidisciplinary collaborative longitudinal studies. I think it's huge. And my concern was, is the funding dropping off for these?

Dr. Daniels: Which still may be a concern, especially if they're costly studies.

Dr. Koroshetz: They're definitely expensive. That's for sure.

Ms. Redwood: Yes.

Dr. Daniels: So then our final objective to talk about today is 2.L.B: "Launch at least three studies that evaluate the applicability of ASD phenotype and/or biological signature findings for performing diagnosis, risk assessment, or clinical intervention by 2015."

And the Group felt the last time that the recommended budget had been partially met, and there were more than three studies launched, but that more funding and more work in this area is needed.

And so what do you feel the field has been doing in this area? What's the status? What are the major challenges and needs?

Dr. Minshew: This is Nancy. I think it's still in evolution. Just one example, for example, might be imaging and the need for methods that are even more sophisticated. To identify alterations in the

brain and autism, whether it's structural or functional or DPI or connectivity, just as what, 10 to 15 years ago, retinal connectivity analyses those are the end.

And sometimes I really think we need some support for the evolution of the technology, even if that is embedded within a study of longitudinal change. Because if you want to monitor change in the brain in response to any intervention, we've got to have more refined, more sophisticated measures.

Dr. Daniels: Thanks. Other thoughts about this?

Dr. Koroshetz: Well, I was struck in this element in terms of what was published going from, what we usually see is a single group shows a bio-signature publishes the paper, and then it doesn't really go very far. It stays within the single group.

But the ABIDE study, where they looked at functional connectivity across multiple sites in 964 people was, I thought, a real lesson for the field that this is what you have to do to make the

kind of genesis of how clinically useful something is.

So I thought that was a good step that the field had taken. I don't know. Nancy and Kevin, do you have any comments there that this idea of, you have a bio-signature, but you have to validate it, not just discover it? Doesn't really help the field, you have to go that next step and elevate it.

Dr. Pelphrey: Yeah, I would agree with that. I think Nancy and I were both part of ABIDE. It was a landmark study, but of course, it also is the top end of what all of us can do together, say, Committee work, in a sense.

But I think that just the way it's a validated signature, one would be to show how it responds to a treatment for core symptoms. Yeah, that's the approach that we're particularly interested in. One is to compare at across disorders. All of those speak to, Walter, what you just said and what Nancy said about methods development. Those approaches can be multicenter, multidisciplinary and incorporate methods development along the way.

Dr. Koroshetz: Yeah, I mean my big worry now is, unfortunately, it's not that it's not going to be enough methods, because, you know, people are turning out methods, especially with the connect on project coming along, there's going to be just a plethora of studies looking at different tracks in the brain.

My worry is standardization. And it's so easy to discover something, by chance, I would use these techniques that have low signal to noise and has so much, so many confounders and how the measurements are made and analyzed, that, you know, something like what ABIDE did is really critical to move forward with these new technologies that will be coming out soon.

Dr. Minshew: That's right. And I think across many areas of work, there needs to be, I think, a way of supporting that kind of mechanism. Because ABIDE was really a grassroots kind of effort, don't you think, Kevin?

Dr. Pelphrey: Yeah, absolutely. Wearing two hats, on the one hand, it was sort of exciting to see what all of us could do, you know, with having

been funded by NIH and Simons Foundation and Autism Science Foundation, and other places, we had already collected all of that data. And then without additional funding, we were able to produce a -- you know, I think -- a really elegant paper.

But sort of putting my taxpayer hat on, I would like to see a lot more of that, rather than asking for more support to do something that I think that we should all be doing as a rule, combining our data and being much more collaborative.

Dr. Minshew: Well, I would say it's not that scientists won't collaborate. This isn't the first -- ABIDE isn't the first -- demonstration that people will get together, dump all their data on the table, and try to mine it. It's just that there have to be people who are supported to do that.

And Adriana has the benefit of product foundation support. You know what I mean?

Dr. Pelphrey: Yes, absolutely.

Dr. Minshew: You know, it's going to happen.

There are some other systematic issues that have to go on.

But at any rate, I think the whole point that we've made is that we need to somehow figure out how to take the data that individual groups collect and pool it together to address particular issues, however that's going to be done. Because, you know, having 25, 50, or 75 is no longer going to be enough.

Dr. Daniels: And that does overlap a little bit with some of the discussions from this morning on Question 7 about standardization of data and methods and so forth. So I think in the workshop you might get some input from some of those people that are on that Planning Group as well.

Dr. Minshew: And it seems on that issue there are, to me, two parts of it. There's got to be a component that is moving ahead with methods development and discovery and then a component that standardizes methods at a point in time that collects data to answer questions. But I think lots of times, we mix those two together. And it becomes hard, often. Just one or the other is

under-supported. You see what I mean?

Dr. Daniels: Yeah. I'll note that. Anything else?

Dr. Minshew: It seems to me --

Dr. Daniels: What, go ahead.

Dr. Koroshetz: It's usually that pooling and validation that's not supported, because discovery stuff is, you know, sexy and easier to get funding for. It's actually to the hardcore grunt work of, you know, validating something that's, you know, already been published that's actually usually harder to get support for. But it's incredibly important.

Dr. Minshew: Right. The whole translational piece after that even is, I think, under-supported. Looking back over a couple of decades of work, I see so much progress in the science. And yet translating that science into changes in practice and policy is slower, in part because there's less support for that translational effort. At least that's what it looks like to me.

Dr. Daniels: Good. So any other comments on this one?

Ms. Redwood: Just that the part about clinical intervention, I think there's really -- I mean, when you look at all the science that we have, we still are lacking in terms of the clinical interventions that we have. So that, I think, really needs to be a focus.

Dr. Daniels: And at the bottom of your sheet, you'll just see the category that was not specific to any objective, otherwise known as "Other," and now, maybe moving to another name that will be determined by the Committee, possibly "Core Activities" or something along those lines, which represents the work that's being done that didn't fall into the objectives. And the objectives were created by the Committee to address gap areas. So there was a body of work that was being done before the Strategic Plan came into existence. And that continues on as a foundation for other ongoing efforts. So that's represented here, and that's what that funding is for.

So you've successfully made it through the discussion of each of these objectives. The final part of the call today is going to be discussing

the aspirational goal for Question 2, which is "discovery, how ASD affects development which will lead to targeted and personalized interventions."

And we want to have you all discuss, how far have we come in 5 years toward meeting that aspirational goal? And where have we made progress and accomplishments? And where are we still challenged with things that need to happen? And are there barriers that we need to overcome? So what do you all think?

Dr. Koroshetz: Don't know where to start, so many barriers --

Ms. Redwood: I don't think we've met it.

Dr. Koroshetz: -- I don't have any -- in terms of treatments, I'm not aware of any effective treatments [Inaudible comment] effects.

Dr. Minshew: What about the Denver Early Start model? Does that not count toward this?

Dr. Pelphrey: This is Kevin. I would second Nancy's nomination for the Denver Early Start, particularly the paper, I guess it was 2012, that Jerry Dawson's group put out, showing, you know, differences in brain function as a result of Early

Start Denver model.

Yeah, it was flawed somewhat in that they didn't actually have a baseline and outcome condition, but they were able to show group differences from expected normal with the Denver Early Start model. You know, selfishly, our group published a study showing that a comparable behavioral measure pivotal response training affected brain development in a case series of on subjects.

But there's more and more interest in doing these types of treatment studies that involve neurophysiology and imaging as outcome measures -- interest in personalizing that, starting first at group variables like male/female and then looking at, when possible -- so, for example, in the context of our ACE network, looking at how genetic data can predict treatment response and, you know, compounding that with the text of the participants and evaluating it within the chain.

So stuff is coming along. And I think it's really well positioned as a goal, because it's what people are quite interested in. But a lot

more needs to be done and we are nowhere near adequately to address that goal.

Dr. Minshew: That's right. I think there's a lot to do. But I also like the paper that came out this year or last year comparing different approaches to preschool intervention that showed that outcome was pretty much equal as long as it was a good program with good leaders.

Dr. Pelphrey: Yes, that was really cool.

Dr. Minshew: The paper – yeah -- the paper about how peers in school-age children were more affected than the previous traditional co-op therapy in improving social function.

Dr. Pelphrey: Yeah. That reminded me--

Dr. Minshew: And then finally -- yeah?

Dr. Pelphrey: -- yeah, that reminded me of [Inaudible comment] work.

Dr. Minshew: And then finally, that having the job for adults resulted in documented improvement in executive function and, I believe, working memory. So it's not that we have nothing. But we're starting to get some nice things. We just need a much larger translational medicine, or

whatever you want to call it, scale so that we do actually have an impact on everybody's daily life.

Dr. Koroshetz: I don't know if this is off topic. But we talked about trying to understand the biologic mechanisms under the regression. Is there -- are there people interested in studying the biological mechanism underlying improvement?

Dr. Minshew: Yes. We have a study in adults where we have a neural cognitive intervention. It's 18 months long. It's funded by NIMH and DoD and Autism Speaks. We're about a year from ending, 18 months. And we do have fMRI measures that are relevant to the intervention areas.

So I think that's certainly the trend that's coming along, is design an intervention and then have imaging measures as well as cognitive behavioral measures of change. So, and you see that in the at-risk infants as well. But there's still a lot more to be done.

[Pause]

Ms. Singer: Hello?

Dr. Daniels: Yes.

Dr. Minshew: Hello?

Ms. Singer: It just got super quiet there for a second.

Dr. Daniels: We're still here.

Dr. Minshew: It's the sound of thinking.

Dr. Daniels: Any other thoughts about areas of development that aren't yet understood enough to help with this but are great needs?

[Pause]

Dr. Koroshetz: Anybody, thoughts about something that was brought up? There were a couple of things brought up in the gap areas in the last Plan. One of them was to look at noncoding genes, noncoding RNAs. Another was to take a variance of IPS cells, looking for phenotypes in patients with autism. Another was trying to look at the environmental interactions in the microbiome projects with autism.

Any of those ring a bell to anyone as important? Anything done in those areas?

Ms. Redwood: I think there's a lot of interesting work coming out with the microbiome and links to the immune system.

Dr. Pardo-Villamizar: Yeah. I think that this

is a very exciting area. And there is a lot of work, I believe, in animal models now about how early infections for early changes in the environment of the gastrointestinal system influence the future immune system and actually influence how the immune system is going to shape in the future for potential problems of autoimmunity or even to responses to infections. So again, this is a fascinating area, although it's still under development.

[Pause]

Dr. Koroshetz: Any other gap areas that people want to bring up in terms of Question 2? Like the biological mechanisms underlying autism? What are the areas that may be promising for research now?

Dr. Minshew: I think the rTMS methods may have considerable potential. And I think there are studies already being done and advanced but perhaps not a lot. I think that would be a worthy goal.

Dr. Koroshetz: I am sorry, so what's the rTMS? What does that refer to?

Dr. Minshew: It's regional transcranial

magnetic stimulation.

Dr. Koroshetz: Oh, I see. Yes.

Ms. Redwood: You know, Walter, one of the areas that I think has been under -- you know -- one of the things we're not doing a good job of is coordinating some of the science, you know, to really look at what the mechanisms are and using some type of systems biology approach to try to plug in the science that we have now.

You know, it seems like a lot of the science is happening in silos, with the immune system and the GI system and the neurological system. And so if there was a way where we could cultivate more of a systems approach to looking at the science we have so far, it might help more with identifying these underlying mechanisms—just a thought.

[Pause]

Dr. Koroshetz: Okay, Sue, so what do you think? I think we did a good job, don't you think?

Dr. Daniels: Yes, I think so. Anything else on the aspirational goals? Any left? Any comments you might want to make about how we've done in that area?

You've done a great job going through the Plan and giving us some thoughts about ways that the science has advanced and other areas where there are still great needs. So I think this has set us up well for the workshop.

I will be sending out more information about the next steps and information about the workshop. And we will all be together in a room. And all the invited experts, all the IACC members will be able to engage in discussion. And anyone will be welcome to provide comments.

But we only have less than an hour for each of these individual topics, which is why the phone call was so important, to be able to have a little bit more time to get some thoughts out. And we will have to be a little bit more focused during the time of the workshop to be able to get through it all.

But hopefully there will be some cross-fertilization as well, because you'll be able to comment on some of the other objective areas -- other question areas in the Plan.

So, what do we --

Dr. Koroshetz: The workshop? I mean, do we -- in terms of the Group going into the workshop, are there things that we need to prepare in advance or delegate or topics or things like that?

Dr. Daniels: I will send out some information. So initially, we're writing some summaries up. And so we need to see -- we have hardly any time before the workshop. And I don't know that it's realistic to expect write-ups to come in before the workshop.

So I'm going to work on a plan for that and making sure that we get our write-ups. But I think they will be due after the workshop, unless anybody here has objects to that, so that it gives you a little bit more time. And then hopefully you can incorporate more of it.

But our Office has been trying to put a lot of the information together, at least initially, to give you something to go on. So hopefully it will make your job easier. So what we're going to do today is we're going to go through this table and fill in more information based on this call and give it back to you so that you have it. And then

we'll have a larger discussion on Friday.

And we have -- from the last time, Walter, you had volunteered to do the initial write-up. And then the shutdown happened, and we didn't get to be able to finish that. But we will want a volunteer to do the write-up for this. And so if you're still willing, perhaps after the workshop, we'll have to -- we'll be able to get that in from you.

Dr. Koroshetz: Yes.

Dr. Daniels: But we'll give you more instructions and guidance and so forth on that.

Dr. Koroshetz: Do you think that will be 1 hour at the workshop to discuss Question 2?

Dr. Daniels: Yes. So we will go through each of the questions. We'll have a little bit of an introduction. And then we will go through each of the questions in order. We'll have a working lunch to try to save some time. So we will get our lunches that -- everyone will need to buy their lunch -- and we will have it come onsite so that it will be easy to buy.

And then have everybody sit back down and go

through the rest of the workshop. We will have public comments, finish all the questions. And then we'll have a synthesis session at the very end before everyone adjourns and goes home. So that's the plan.

It will be kind of compact, but this area is pretty big. And probably no matter how much time you attempted to put into it, you probably couldn't cover everything. So we'll just do our best.

So I'll be in touch with more information. Are there any other immediate questions anyone has?

Dr. Pelphrey: No.

Dr. Daniels: Well, thank you so much.

Dr. Pelphrey: Thank you.

Dr. Daniels: We really appreciate everyone being on the call. We appreciate the contributions of our invited participants, as well as the IACC members and our listening audience. Thanks very much and we're adjourned.

Ms. Singer: Thank you, Susan. I just want to stress that OARC did a lot of work putting this together for all the groups, and we really

appreciate it.

Dr. Daniels: Thank you.

(Whereupon, the Strategic Plan Question 2 Planning Group of the Basic and Translation Subcommittee was adjourned.)