U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

SUBCOMMITTEE FOR BASIC AND TRANSLATIONAL RESEARCH

MONDAY, NOVEMBER 26, 2012

The Subcommittee met via webinar at 12:00 p.m., Eastern Standard Time, Geraldine Dawson and Thomas Insel, Co-Chairs, presiding.

PRESENT:

THOMAS INSEL, M.D., Co-Chair, National Institute of Mental Health (NIMH)

SUSAN DANIELS, Ph.D., Office of Autism Research Coordination (OARC), National Institute of Mental Health (NIMH)

GERALDINE DAWSON, Ph.D., Co-Chair, Autism Speaks

ANSHU BATRA, M.D., Developmental Pediatrician, Our Special Kids

LINDA BIRNBAUM, Ph.D., National Institute of Environmental Health Sciences (NIEHS)

COLEEN BOYLE, Ph.D., M.S. Hyg., National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC)

NOAH BRITTON, M.A., Bunker Hill Community College

MATTHEW J. CAREY, Ph.D., Left Brain Right Brain and other Autism Blogs

PRESENT (continued):

TIFFANY R. FARCHIONE, M.D., Division of Psychiatry Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA)

ALICE KAU, Ph.D., Autism Spectrum Disorders, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (NICHD) (for Alan Guttmacher, M.D.)

DONNA M. KIMBARK, Ph.D., Congressionally Directed Medical Research Programs, Department of Defense (DoD)

WALTER J. KOROSHETZ, M.D., National Institute of Neurological Disorders and Stroke, National Institutes of Health (NINDS)

CINDY LAWLER, Ph.D., National Institute of Environmental Health Sciences (NIEHS) (for Linda Birnbaum, Ph.D.)

LYN REDWOOD, R.N., M.S.N., Coalition for SafeMinds

JOHN ELDER ROBISON, Self Advocate, Parent and Author

ALISON TEPPER SINGER, M.B.A., Autism Science Foundation

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In many cases throughout the transcript, two or more speakers began to speak at one time, causing interruptions. When this occurred, it was denoted by dashed lines.

PROCEEDINGS

12:07 p.m.

Dr. Daniels: Hello and welcome to everyone on this call of the IACC Basic and Translational Research Subcommittee meeting.

We are here today to talk about the different chapter updates that you all have been working on in my absence. I really appreciate all the work everybody has done to keep everything moving.

Dr. Geri Dawson is going to be helping lead this conversation today. Dr. Tom Insel will be joining us in a little bit.

But, Geri, would you like to say some words of welcome?

Dr. Dawson: Yes, absolutely.

I want to just begin by welcoming Susan Daniels back. We are so glad to have you back, Susan. I hope everything is fine on the home front with your new little one.

Dr. Daniels: Thank you.

Dr. Dawson: But we have certainly

missed you. So, it is great to have you back.

Today our purpose is to review each of the chapters that now have been drafted. We are going to try to go through each one step-by-step. If you open them, you will notice that there are a couple of comments and questions that need to be addressed on each one.

We will start for each one having the leads of that chapter kind of open the discussion. Then, if there are specific changes that people would like to make, or as we respond to questions that are in the comments, OARC will track those changes, so they can know what needs to be done.

And then, at the end of the discussion, we will be voting. If it is clear that it is unanimous, we won't need to do a roll call. However, if it isn't unanimous, we will need to go through and do a vote by a roll call, and then final decision, at least in terms of what will be moved forward for our

December meeting, will be done with the majority vote.

Before we get into going through each chapter, I think that Susan wanted to take roll call.

Dr. Daniels: Yes.

Dr. Dawson: So, let's go ahead and do that now.

Dr. Daniels: Okay. Thank you, Geri.

So, I know that Geri Dawson is on the line.

Is Tom Insel on the line?

(No response.)

It sounds like not yet.

Coleen Boyle?

Dr. Boyle: I am on the line, and I will be getting off in about a half-hour and Cathy Rice will be taking over as the official CDC designee.

Dr. Daniels: Thank you very much.

Tiffany Farchione?

Dr. Farchione: I'm here.

Dr. Daniels: Thank you.

Alice Kau?

Dr. Kau: I'm here.

Dr. Daniels: Donna Kimbark?

Dr. Kimbark: I'm here.

Dr. Daniels: Cindy Lawler?

Dr. Lawler: Here.

Dr. Daniels: Walter Koroshetz?

(No response.)

Not here so far.

Anshu Batra?

Dr. Batra: Here.

Dr. Daniels: Noah Britton?

(No response.)

Not yet.

Matthew Carey?

Dr. Carey: Here.

Dr. Daniels: Dennis Choi?

(No response.)

Not so far.

Lyn Redwood?

Ms. Redwood: Yes.

Dr. Daniels: John Elder Robison?

Mr. Robison: Yes.

Dr. Daniels: Alison Singer?

Ms. Singer: I'm here.

Dr. Daniels: Okay. Great. So, we have a quorum.

Dr. Birnbaum: Linda Birnbaum is on the line also.

Dr. Daniels: Who? Sorry.

Dr. Birnbaum: Linda Birnbaum.

Dr. Daniels: Oh, Linda?

Dr. Birnbaum: Yes.

Mr. Britton: Hello.

Dr. Daniels: Yes?

Mr. Britton: Hi. This is Noah Britton. Sorry, I am teaching, so I am doing two things at once, but I am listening.

Dr. Daniels: Okay. Great. Thank you.

Mr. Britton: Uh-huh.

Dr. Daniels: Then, we just have

Tom, Walter, and Dennis who will be joining us, hopefully, in a little while.

I would also like to make a couple of just really quick announcements that I will repeat at the end for those who are calling in and listening to this call.

The IACC will be having a full Committee meeting by conference call on December 18th from 10:00 a.m. to 5:00 p.m., Eastern Time. And more information about that will be posted on our website, and I will be sending out information to the Committee members. But I just wanted you to have that date on your calendars.

And then, there will be a full IACC meeting in person on January 29th, which is also a Tuesday, here in Washington, D.C., actually, in Bethesda, Maryland, at the Natcher Center on campus at NIH.

And so, I just wanted you to have that information. All the information will be posted on our website and will be emailed out

to people through our listserv.

So, with that, I will turn it back over to Geri.

Dr. Dawson: Okay. Well, first of all, I wanted to thank the leads of each one of these chapters for all of the work that they have put into drafting these. I think they are really in great shape. I know that a tremendous amount of work went into these. So, I want to thank everyone for their time.

I also wanted just to clarify a little bit about process. So, the final vote in terms of these updates will be made at the December 18th meeting. And so, the voting today reflects the opinion of our Subcommittee in terms of our feelings about these drafts going forward to that final December 18th meeting.

I also just want to have everybody keep in mind that these are supposed to be just updates. We are not trying to rewrite the plan to reflect a lot of new priorities

and ideas that people have and are eager to share, but, rather, we are trying to do a simple update of what happened in the last year and what new gaps have arisen in the last year.

So, I think we should try to refrain from -- you know, try to open up to broader overall changes in strategy, and so forth, because people will have plenty of time to do that in 2013.

Susan, is there anything I am missing that I should add before we get into talking about Chapter 1?

Dr. Daniels: Only that our goal is to complete this version of these drafts to go forward to the full Committee, and then, hopefully, to be approved and finalized by the full Committee on December 18th, and then moved forward into a final document. And so, we hope to finish that in calendar year 2012, if possible.

Dr. Dawson: Right. So, looking

at it, we have five chapters to do. Susan, maybe you can help us stay on time because we probably should keep the discussion of each to about 25 minutes or so, so that we don't end up running out of time at the end and not having time to discuss the later chapters. So, we may have to at some point just cut off discussion, if we have to, and just take a vote. Hopefully, we will have time to fully discuss everything.

So, with that, maybe we should then start with Chapter 1. You should have all received the draft of that.

I would just like to open now the floor to the leads.

Mr. Robison: Yes.

Dr. Dawson: You could start walking us through the remaining questions that need to be addressed. And then, we will open it up to fuller discussion by the rest of the people on the Subcommittee and get this one finalized.

So, Chapter 1.

Mr. Robison: Yes, is it John Robison here.

Well, in the first part, prevalence, I think that we are all set with that, I think.

Then, going down into diagnosis, the second section, we have a note here that we are going to cite the first of the DSM validation studies. And, Geri, you just emailed the actual study information. So, we will add that to answer our comment.

Now we have something that is missing there. After we talk about the DSM validation study, I had also written a paragraph saying that the DSM-5 group has identified a new disorder, social communication, whose stated intent is to capture individuals at the least-disabled end of the autism spectrum that are not captured by the ASD diagnosis.

We are concerned that no services

have been identified for those people and whether, indeed, that should be part of the autism spectrum.

So, I think that that somehow just got lost, but I think that we had talked about putting that in during our last conference call. And it was my expectation that it was going to immediately follow the first paragraph in diagnosis.

Then, the rest of diagnosis I think we are okay with.

Early screening and detection, I think we have sort of trimmed that down.

Early diagnosis, you know, the only thing we had there was the Wolff study where we talked about possibly detecting autism before behaviors emerge in the first year of life. I guess I would vote for leaving that in, even though it appears in Question 2 also.

And I feel the same way about the Bosl study, which is the last paragraph of

that section.

Then, in what gaps have emerged in the past 18 months, the only question we have here is the paragraph in which we say, "Some studies show that adults with autism continue to be socially-disadvantaged and have significantly-lower academic and career attainments as compared to non-ASD adults in similar surroundings. Autism is a lifelong disability. Yet, research efforts to date have focused primarily on childhood and adolescent detection and intervention. More emphasis must be placed on adults of all ages."

So, the question there is, should this be moved to Chapter 5. I feel strongly there that it belongs in Chapter 1, even if it repeats what is in 5, because I think that is a very strong statement and it properly belongs in the first part of this report, right where the public will see it first, not all the way at the end at Question 5.

And I think that it is, indeed, a gap in detection and when I should be concerned, and it is properly placed in Question 1.

And then, that takes us to the end. We have 1400 words and then we have the references. That is what we have. With the exception of that missing paragraph, I am satisfied with what we have.

Dr. Daniels: John, this is Susan.

Is the third paragraph under the gaps the missing paragraph you are talking about? I think that Dr. Insel may have moved it.

Mr. Robison: I am sorry, yes. Yes, you know, he did say that, and I see it here. Yes, it is there. It is okay.

Dr. Daniels: Okay. Good.

Dr. Birnbaum: This is Linda Birnbaum.

I just want to say that your couple of questions about the potential

repetition, for something that we want to make a point on, I think it is very helpful to have it in more than one place.

Mr. Robison: And I would say, too, that this is a significant change in position because the Question 1 in every previous iteration of this report has been exclusively focused on diagnosis of young children. And now, we are recognizing for the first time in a published report that “When I should be concerned” applies to when you should be concerned about a person discovering they have autism at any point in their life.

Dr. Daniels: John, just as a historical note -- Susan Daniels -- that was discussed by the Committee on a number of different occasions. And on this last revision of the Strategic Plan in 2011, they made a very deliberate attempts to try to keep all the adult references to Chapter 6, but they did talk about having adult diagnosis in Chapter 1 and the previous Committee felt that

they preferred to keep it all in 6. So, that is why it is not there, just for historical --

Mr. Robison: Well, I guess what I would say in response to that, Susan, is that the decision to put it where it was last year probably resulted in many people like me thinking that it was overlooked, rather than repositioned. I think it is a very, very important thing, and it properly deserves to be right there in the beginning.

Ms. Singer: Can we maybe think about, instead of saying "more emphasis must be placed on adults of all ages," saying, "persons of all ages"? So that it recognizes that --

Mr. Robison: Sure. Yes, I would say, "individuals of all ages".

Ms. Singer: Okay.

Mr. Robison: Yes, why don't we just say, "individuals of all ages"?

Ms. Redwood: This is Lyn.

I somewhat agree with Susan, being

on the IACC previously, that we keep this in Chapter 5. I don't think because it is not in the very first chapter that it in any way belittles the comment. And it shouldn't be viewed that way, that if it is in the first chapter, it is going to get more acknowledgment.

Dr. Birnbaum: I am a little confused. This is Linda Birnbaum.

I just think that repetition is not a problem and having this in both places isn't a problem.

Mr. Robison: I think so, too.

Dr. Daniels: It is Susan.

I wasn't stating an opinion. I was just trying to tell you the background of why it became that way. But it is up to the Committee what they would like to do from this point forward in terms of what you would like to see in this draft.

Dr. Carey: This is Matt Carey.

I think I am with John on this

one. I mean, I think it is appropriate in this place. You know, “when should I concerned?” Yes, I think it has always been taken as I -- there has been kind of the voice of the parent in there, but there are a lot of "I's" on there who are unidentified adults. I think it is very valid to have it in here.

Mr. Robison: Yes, I just think we are not talking about much repetition, and I see no good reason to omit it here, even if it is present at the end also.

Dr. Dawson: This is Geri.

I think another point is that we still know so little about diagnosis in adults and still haven't done very many good prevalence studies in adults. The diagnostic systems don't quite work well with adults.

So, I think by highlighting it here it does reflect a very significant gap in our knowledge. So, that is probably a good thing to highlight in both places.

Ms. Redwood: Geri, this is Lyn.

Then, should it not say, though, that we do have gaps in being able to diagnose adults? It is the way that sentence is worded.

Dr. Dawson: Yes. And let me look at the gaps here.

Ms. Singer: Well, if we are going to include adults in Chapter 1, do we need Chapter 5?

Dr. Dawson: Yes, because that is about services and supports and a lot of other broader issues that aren't specifically around diagnosis prevalence.

Ms. Singer: But if the decision is being made to include adults throughout the plan, which is a new decision for the IACC, then maybe we shouldn't, then, call out the population of adults as being different if we are including them as being the same.

Dr. Dawson: I am wondering, Alison, if that is going to be more of an overall strategy decision, rather than an

update. So, I hear your logic there, but that would necessitate a great amount of changes all across the different questions. I am not sure if we want to try to take that on at this late date. But I think, looking at 2013, that to me seems a very reasonable question to come back to. That would be my opinion.

Dr. Boyle: This is Coleen.

I was going to say the same thing; that might be a major change in our restructuring that we can think about in 2013.

Ms. Singer: Okay. That is fine.

Dr. Dawson: So, I sounds like, well, before I try to move to getting us to get this one in the bag here, so that we can go on to some of the others, are there any other major issues or minor issues that people would like to bring up, any wording or --

Ms. Singer: I had a couple.

Dr. Dawson: Okay.

Ms. Singer: In the second paragraph, where it says, "The ADDM Network

released their most recent data," I think it should be "its most recent data" since "Network" is singular.

I also had a question about the diagnosis of social -- where is the --

Dr. Dawson: Down under gaps.

Ms. Singer: Right. So, in the third paragraph under gaps, where it talks about social communication disorder, in the last sentence where it says, "There is a fear that it will be interpreted as `mild ASD without supports,'" I was confused about the term "mild ASD without supports" since mild ASD refers to diagnosis, and without supports refers to intervention. Should that be "without need for supports"? It is not an adjective. So, should that say, "will be interpreted as `mild ASD' without need for supports"?

Dr. Dawson: Or how about "without well-defined supports"?

Ms. Singer: But supports is an

intervention. So, I don’t understand how you would use supports to describe a diagnosis.

Dr. Dawson: Maybe John wrote this, so maybe he should be the one. But I think the idea there is that since, unlike Autism Spectrum Disorder, this new condition doesn't have specific prescribed treatments, there has never been any intervention studies or any even guidelines, clinical guidelines about how you would serve the population, it is worrisome that it wouldn't get supported.

Mr. Robison: I think, having written that paragraph, I would say, just as you just suggested, that the words should be, "There is a fear that it will be interpreted as mild ASD without the need for supports" because I think you are correct that supports is the intervention; ASD would be the diagnosis.

I think it is appropriate to say that you have a diagnosis without the need for

supports, and that I think is the concern we wish to express. So, I would just say change "without supports" to "without the need for supports".

That is what you think, too, right, Alison? That was your --

Ms. Singer: Yes, then it is a diagnosis.

Mr. Robison: Right, yes. So, it is mild ASD without the need for supports.

Dr. Boyle: And I would just get rid of the quotes.

This is Coleen.

Mr. Robison: Yes, I would agree with that, too. We don't actually need quotes around it.

Dr. Dawson: Okay. Are there any other suggestions for Chapter 1?

Dr. Batra: This is Anshu.

Just a very minor adjustment in the second paragraph under prevalence, where it states that "the surveillance data showing

prevalence is 1.1 per 100 children," changing that to "1 in 91 children" because I think that number, it is hard to wrap your brain around the 1.1 child.

And the same with the third paragraph, the Korean study, 2.6.

Dr. Boyle: We could put percents there, prevalence of 1 in 88 or 1.1 percent, something like that.

This is Coleen.

Dr. Boyle: That is fine. I am okay with that.

Mr. Robison: I would agree that 1 in 88 or 1 in 91, or whatever, is more understandable to the lay public than 1.1/100. I think that is a good suggestion for readability.

And I would suggest we use that philosophy throughout this report, actually, because it does make it more accessible to the average person.

Ms. Redwood: Should there be

something in there regarding that particular paragraph in terms of the age of the children now? Because I am afraid that that might be interpreted as what the current rate is now on the ground; whereas, actually, that data is like a certain cohort in 2000, so 12 years old.

Dr. Boyle: We can add something about that.

Dr. Dawson: Do you want to go ahead and offer some language, so that Susan can have that, because she is tracking these changes for us?

Dr. Boyle: Sure.

Dr. Dawson: Or send them.

Dr. Boyle: Yes, I will send something. I am not actually at a computer.

Dr. Dawson: Okay.

Dr. Daniels: That is fine.

Ms. Redwood: It might also be important to put in the gap area, too, that we really need more current numbers or a better

way to be able to track the prevalence.

Dr. Carey: This is Matt Carey.

One other thing, "prevalence," the last paragraph, I think you could say, "These studies suggest that some, but possibly not all increase prevalence," because at this point there is nothing -- I don't think it is definite. You could say that possibly not all is due to some other social factor.

Mr. Robison: I think we already had that discussion. Certainly, myself and Dr. Insel and Geri did, and I think we made the decision earlier to say, "some but not all" instead of "possibly not all". I think that he actually had written about that earlier in the year.

Dr. Dawson: Well, and I think the word "suggests" also softens it rather than if we had used the word "indicates," that would be different. But this is just saying "suggests".

Mr. Robison: Yes, I guess I

feel like Dr. Insel and I talked specifically about that wording and sort of agreed on what we have. And I feel comfortable standing with that. I don't guess I think that we want to -- I don't know. I am okay with it.

Dr. Dawson: Are there any other suggestions?

(No response.)

Okay. Are we ready to vote on this one then?

Dr. Daniels: Geri, this is Susan.

Let me go through the changes, just to repeat them for people, so they can follow along.

So, I have heard that we are going to be changing some of the wording in the second paragraph, the "1 in 88 or 1.1 percent".

Coleen is going to send an additional statement to add to that.

The South Korean study, we will also add the percent and the number in the

third paragraph.

In diagnosis, we are going to add in the references that are requested there.

On page 3, the American Psychiatric Association, the third paragraph under what gaps have emerged, that has been moved, and it is fine. Oh, but it will be changed to say "mild ASD without the need for supports", removing the quotes.

In the last paragraph or the second-to-last paragraph on that page, "More emphasis must be placed on individuals of all ages."

And I think that was the last change that I had. So, if that sounds accurate, then we are ready to vote.

Mr. Robison: It sounds accurate to me. John here.

Ms. Redwood: Susan, I also made the recommendation that there be something in the gap that also talked about the need for getting more rapid prevalence data than what

we have now.

Dr. Daniels: Did someone have particular language to offer on that?

Dr. Boyle: This is Coleen.

I can put something together, a sentence or two.

Dr. Daniels: Okay.

Dr. Boyle: Okay?

Ms. Redwood: That would be great because I think that is an important gap. When we have data that is 12 years old, I think that is something we need to address.

Dr. Daniels: Okay. So, Coleen will provide that.

Dr. Dawson: So, Susan, do you want to call for the vote then?

Dr. Daniels: Why don't you get a feel for whether we are likely to be unanimous? Because I won't need to do the roll call if we are unanimous.

Dr. Dawson: Okay. So, is there anyone at this point who is not going to be

comfortable voting in favor of the suggested revisions and this going forward to the December 18th meeting?

Mr. Robison: This is John here.

I am comfortable with the revisions, and I am also comfortable with the suggested addition that we identify slow arrival of prevalence data as a gap that needs to be closed.

Dr. Dawson: Is there anyone who does not feel comfortable with these changes and would not vote in favor?

Dr. Insel: Geri, this is Tom Insel. Sorry, I have been on mute, but I have been listening in.

I agree with all of the proposed changes. I want to emphasize the need to say something about that the prevalence numbers that we have represent the 2000 cohort because I think that has been misunderstood by many people. But I understand that that is already being added. So, that was my only addition.

Dr. Dawson: Great, and welcome, Tom.

Okay. Susan, I think we are ready for the vote.

Dr. Daniels: Okay. So, all in favor, vote aye.

(Chorus of ayes.)

All opposed?

(No response.)

Any abstaining?

Ms. Redwood: This is Lyn.

I am going to abstain because I still have concerns about putting things in different chapters and having them be redundant.

Mr. Robison: Well, we decided we weren't taking anything out of this chapter, Lyn. We were leaving it in.

Ms. Redwood: Yes. No, I know that, John. That is why I am abstaining.

Mr. Robison: Oh, that is what you don't agree with? Okay.

Ms. Redwood: Yes.

Dr. Daniels: Okay. So, Lyn, I have got you as an abstention, and then everyone else is in favor.

So, with that, the motion carries, then. There wasn't really a motion, but, hopefully, we will do it better next time. We will go for this as being the final version of Chapter 1 to the full Committee.

Dr. Dawson: Great.

So, Tom, would you like to take over?

Dr. Insel: Geri, you have been doing a great job. Why don't you continue, and I will join in as necessary?

Dr. Dawson: Okay. All right. Well, feel free at any point to take over.

All right. So, let's move on, then, to Chapter 2. This is "How can I understand what is happening?" And if you look at the questions, there is a question about whether we should add the paper from

Pediatrics on noting the lack of effect of gestational infection, whether that should be added.

Other than that, it looks like -- let me see if I am missing anything else -- it looks like it is in pretty good shape. And so, I am going to turn this over to the lead on this one, and you can walk us through this one.

Dr. Koroshetz: Hi. This is Walter Koroshetz.

So, I was aided by Alison Singer, Dennis Choi, Carlos Pardo, Kevin Pelphrey, David Amaral, and input, also, from Beth Malow.

So, unfortunately, it is still fairly long, but it is about half as long as it started because we thought that there had been quite a bit of progress made over the period of time over which we have been looking.

We couldn't really deal with all

of them, and we tried to bin things to make it easier for the reader. And so, there were basically certain areas that popped up that were highlighted.

The first of those really related to neuroimaging findings, that there has been, I think, a large growth in using high-technology imaging to study autism. A couple of these studies have kind of opened doors, I believe, with regard to looking at neuropathways that differ between typically-developed and autistic children.

These are the diffusion weighted imaging studies that can look at white matter tracts in a way in which no one could really do except for the last couple of years. So, there have been studies looking at differences in white matter architecture.

One of those studies claims to show differences in 6- to 24-month-olds, though in periods of time where it may be at some point possible to diagnose the changes in

brain, even before symptoms become apparent.

There are also studies looking at the morphometry of brain, the volume of brain. This has been going on for a while. Some of the new studies came out. David Amaral's group looked, showing in his study that the increased brain growth was primarily in those boys with regressive autism, not in girls and not in boys without the regressive autism. So, maybe a marker or a phenotype there.

And there was another study from Israel that did not see in their largest study a macrocephaly as a common feature. So, there is still some controversy in the area.

Functional magnetic resonance imaging is used to study circuits in the brain. One can see areas of the brain activate when tasks are given to children. And a number of papers came out claiming that they can see differences between children with autism and typically-developing children and particular brain circuits involved in social

processing.

And also, some of the structural imaging studies I mentioned before are now starting to look at the language areas and auditory processing in autism. Two studies have found aberrant or certainly differences in the white matter pathways connecting language areas in the brain.

In terms of neurophysiological studies, these are studies trying to look at, basically, how you can examine brain activation using measurements such as EEG or magnetoencephalography. One study did find, using these techniques, atypical audiovisual speech integration in infants at risk for autism. So, we highlighted that one.

We next moved to another separate area which is the molecular basis in phenotypic autism. So, in many of the phenotypic or syndromic autisms, there is a gene that has been identified. Often, there is a monogenic cause. This allows people to

study what that gene is doing, what the protein it encodes for may be doing. So, it kind of gives the tools in which to study the biology of autism, which is what this chapter is concentrated on.

And what we point out is that in many of the monogenic causes of autism, although the genes are different, there is a convergence in many of the studies on synaptic function. And also, there is an interesting point that these raise, that many of the abnormalities in the models of these monogenic disorders are reversible.

So, the dysfunction seems to be the synaptic level, and that altering synaptic function may actually attenuate the symptoms. So, really providing some hope that in autism, if we get to the bottom of these synaptic abnormalities, these may in large part lead to treatments that can help people who are already affected.

Similarly, in a lot of the genome-

wide studies, isoforms of genes have been identified associated with autism, not with high risk, but these have also often kind of come down to synaptic function proteins, such as the large complexes at the synapse Shank.

And studies have, then, shown that these also now in biological models in mice alter synaptic function and glutamate neurotransmission. So, again, the importance here is that the monogenic and the large genome-wide association studies all seem to be pointing in the same direction.

We identified a study which actually kind of combines the genetics with the imaging. It is Met Receptor Tyrosine Kinase gene, which has been associated with autism. It actually has a number of different isoforms. Even in typical children and adolescents, one can see with functional imaging that the isoforms of this gene actually affect how the circuit works. And it is even more different in people with autism.

So, it is an example of how you go from a gene abnormality to a biological effect and then actually back to the people again.

The next area we thought was important was the studies that have been done in gene expression postmortem brains with autism. They have showed, interestingly, again -- it is redundant, but I think it is important -- that, again, here many of the gene expression changes in autism brain again came back to synaptic functional differences. So, I think that also highlights the theme here.

The second part of this study, however, showed that there was a whole of gene expression changes that had never been seen before in the GWAS studies. These all seemed to be linked to immune and glial gene expression in autism brains.

So, an example of how potentially -- well, one theory is that they picked up some of the environmental influences that

occurred in autism affecting the immune system. So, things that would not have been seen in generic studies, because they are basically environmentally-linked, but the link to the autism may be potentially through abnormal immunity.

And that leads into the section on immunity. There have been a number of studies showing that immune abnormalities produced in animal models can give behavioral abnormalities similar to, well, not similar, but somewhat related to what is seen in autism.

And also, the idea of maternal antibodies mediating autism through the placenta affecting the fetus is an area that has also been studied both in humans and in animals. This, again, highlights the immune system.

And the one thing that happened not directly related to autism, but in the last year, is that the immune system has been

discovered to be a major sculptor of synaptic strength. So, this is about the synapse and autism, and immunity may actually be very closely related to synaptic function. The immune system in the papers we have referenced here talk about how the immune system is really the mechanism in which the brain is eliminating redundant synapses that are not necessary, allowing the ones that are key to strengthen while pruning the cells.

The final section is on co-occurring disorders. There have been interesting studies showing that some genetic abnormalities lead to both epilepsy and to autism. We did put in -- and this is up for discussion -- we put in a mention to the fact, which is really an epidemiologic study of the link between autism and GI disturbances. This is a little bit out of the biology piece, but it is here. I am not sure if it should be here if it is also in another section.

And then, Beth Malow also gave us

some very interesting information on recent studies on sleep and the biology of sleep, and how it could affect behavior. So, this is not an epidemiological study. It was basically sleep biology and how it could interact with autism.

In terms of the gaps, the first one I think we point out is the paucity of studies related to the cellular neuropathology of autism, and we point out the need for postmortem tissue to move this field further and to increase importance now, given the loss of brains that occurred after the trouble in Boston.

We also pointed out that the area of induced pluripotent stem cells in which neurocells can be actually made from the skin of people with autism by just taking a skin biopsy, a very complicated procedure, but you can actually develop neurons from skin cells now. There is very little that we could find going on in this area in autism, except there

was one interesting study of Timothy syndrome where they actually were able to do this and nail down a phenotype in the cell culture that is exactly what you would have expected from knowing about the disease. So, it was kind of a teaser that in Timothy syndrome it really worked well, and there should be kind of greater work in this area.

We also talked about the business about the imaging, how things are conflicting in the literature. Some of it may be the fact that people are looking at different time points, and what we really need, since this is a dynamic process, is we need longitudinal studies to plot out these changes in brain structure and function over time, because you can be fooled by picking one time point. It may be completely different if you look at a different time point and you kind of miss the real big picture.

We also mention the need to continue work on females in autism and

underscored again the immune system as an area that there is a lot of progress in, but a lot to be done.

So, that is basically how we kind of thought this through.

Dr. Dawson: All right. Thank you, Walter.

So, let's open it up for discussion. I have a couple of studies that I am aware of that we might want to add, but before we get to that, let's open it for broader discussion from the rest of the group.

Dr. Koroshetz: Give us more space; we will update it.

Dr. Dawson: Yes, right, I know. That is the problem, I suppose.

Dr. Koroshetz: I mean, the question of the comment about including the lack of effective gestational infections, I feel a little bit not clear there, I mean especially given the recent report about influenza may also be related.

Dr. Insel: This is Tom.

I have some general questions for you. I am not sure exactly how to insert this.

But it does seem, especially when you think about the gaps, that as you said for iPS cells, in the last 18-24 months there has just been an enormous set of breakthroughs that are changing our approach to many other related developmental disorders, especially in metabolic disease, in certain forms of cancer, many other areas of medicine that haven't yet been identified or haven't really been studied, so there are huge gaps here.

So, thinking of the Microbiome Project which really delivered in June of this year for the rest of medicine, the ENCODE Project, which has kind of really transformed the way we think about genetics just in the last three or four months, and you mentioned the increasing awareness that the immune system is important for synaptic development,

synaptic plasticity.

But I wonder -- I hadn't thought about this earlier or I would have put in a note -- would it make sense under the gaps to just note in a couple of sentences that, while there is no work relative to autism, we have now this explosion of new tools and new insights that should be applied to autism just the way they are applied to many other biomedical issues. That is a pretty striking gap rather than focusing only on the literature that already includes autism.

Dr. Koroshetz: I think that is a good point. I mean, usually, progress comes when someone builds it. You know, when someone builds a new tool, it helps you solve a problem you couldn't solve before. And so, your thought is thinking to these new tools that have just come and kind of encouraging people from both sides, the tool developers and the autism people, to kind of take advantage. Is that where you are coming from,

Tom?

Dr. Insel: Yes, and also, I think just given what has happened in the last year, just realizing that there are lots of new ways of thinking about neurodevelopmental disorders that have not really been developed for autism. There is a wonderful pair of papers by Chris Walsh's group at Children's Hospital about the importance of looking at somatic mutations in postmortem material, arguing that the actual lesion, if you are looking for a genomic lesion, may not even be apparent in blood. It only shows up in that part of the brain that is affected.

Dr. Koroshetz: Yes.

Dr. Insel: And they provide some good examples, including the paper just published in the last week or two in Cell.

So, that is just a whole different way of thinking about this area that no one has even begun to explore for autism. And, yet, that may turn out to be exactly the right

direction to go in. It is not in the Strategic Plan at this point, I don't think it is, but it would be a good one to bring up.

Ms. Redwood: I was thinking that last year, Tom, there was in one of the sections a reference to the need for work in the microbiome.

Dr. Insel: Yes, I think that is right; there was a mention. I guess at that point we didn't really have what we have now, which is the ATWAS that is available. It is publicly available from the 17 papers that were published in June. And then, there has been a whole series of additional papers since then.

So, that project, which was focused on lots of things but not the brain, really delivered for us over the course of this summer. And to not mention it here as being like an entirely new frontier, and it is, for -- like they just had a meeting last week on Type I diabetes and the microbiome

here at NIH. But we have yet to have anyone thinking about this with respect to autism, at least as far as I know.

Dr. Dawson: Well, actually, we are funding a major study on the microbiome and autism. But, still, it is underway; it is not published. I still think there needs to be more work in that area.

Dr. Insel: Yes, I guess what I am getting at is kind of general point that, as we do this, we want to be thinking about not only what is new in autism, but what isn't new in autism that is new in the rest of medicine that could be important as a gap area.

Dr. Dawson: No, I completely agree. Can you suggest a sentence that could capture this idea of these important breakthroughs and --

Dr. Insel: Yes, what I could do is I think at the beginning of the gap area, because this is all about the biology, I could add a couple of sentences, or maybe just one,

to stipulate that over the last 18 months there have been transformative breakthroughs for the biology, in understanding human development and human biology based on the ENCODE Project, the Microbiome Project, and arguably, some of the work on new sources of variations like the work on somatic mutations or this new area called microchimerism where babies' cells end up in mother's brain, those kinds of things. It is really a pretty amazing number of new insights that were not around 18 months ago.

So, I would be happy to put that in as an introductory sentence in the gap area, just to stress the importance of bringing the autism research fields into line with all the excitement that is happening in the rest of biology.

Dr. Dawson: Yes, I think that is great, and it would really set the stage, too, for thinking about the broader Strategic Plan in 2013.

So, other suggestions?

Dr. Birnbaum: Yes. This is Linda.

At the bottom of the second page, under the molecular basis of phenotypic autism, the last sentence there, the phrase says that "The view that brain immune system responses in autism are likely related to environmental events and not necessarily genetic influences...." I think we really should be moving away from talking about one or the other and stress the intersection of these two.

So, I just think it would be helpful if we reworded that "are likely related to environmental events as well as genetic influences," something like that.

Ms. Redwood: Was that the actual take-home from the paper, though?

Dr. Koroshetz: Well, I think --

Ms. Redwood: Because I remember reading that pretty specifically in the actual

article, that that was one of their conclusions.

Dr. Birnbaum: Well, but I don't think we are necessarily saying that they concluded specifically. I mean, the way this is written, we said, "The researchers found the pattern," blah, blah, blah, and then it says, "an observation supports the view". If that is what they said word-for-word in their paper, yes. But if not, if that observation is something that we are making -- and I think that we have the ability to make it because we are trying to talk about what we know or how we should be looking at things -- I just think it is counterproductive to exclusively say, well, it has got to be one or the other instead of it is probably both.

Dr. Insel: Yes. This is Tom.

I would be hard to imagine how environmental factors would have an impact without working through genetic influences. I don't know any biological mechanism that

doesn't involve changes in gene expression.

Dr. Birnbaum: I think the point of this really, Tom, is that the idea that people think that, you know, it is genes or environment. Instead, almost everything is just going to be -- you know, we know that even things that are very highly-penetrant, genes that are highly penetrant can still be influenced, whether or not you see a phenotype is a function of what happens environmentally.

Dr. Insel: I am agreeing with you, I think. The language should not set up a polarity here. It should clarify that these two things have to work together. They can't be entirely independent.

Dr. Birnbaum: Right.

Dr. Dawson: So, I wanted to see about adding, whether the Committee thinks these papers should be added. I know this is going to be an issue because every week that we wait there is something new that comes out.

But there was a very interesting

paper that came out last week out of Paul Ashwood's group which was, again, looking at immune markers in blood. This was myeloid dendritic cells.

But what was really interesting was that they found that the increased frequency of these was associated specifically with GI problems, enlarged amygdala volume, and severity of repetitive behaviors, and was also more pronounced in children with regression.

So, it was just a very interesting combination of factors that were highly correlated that suggest maybe a particular subtype. Anyway, so that is one paper.

And then, it is one o'clock, and at one o'clock came off embargo three papers coming out in The Archives of General Psychiatry today. One of them I just think is really important because it is the first in vivo study to show microglial activation in the brains of adults with autism. And so, it

was increased microglial activation, and they used PET with a radiotracer to look at microglial activation.

You know, all the studies previously had been with postmortem tissue, raising all kinds of caveats.

Dr. Insel: Is this a Bob Amos study, Geri?

Dr. Dawson: Yes, exactly. I thought that was a pretty important study.

Dr. Insel: Go ahead. Okay. I didn't know this was out. That one, I agree with you, I think that should be in here.

Dr. Dawson: So, those are two I was going to suggest. There are two other papers coming out that also just came off embargo a minute ago in the same issue of Archives. I don't know whether people want to include those or not.

But one of them is a study looking in much more detail at using MRI at kind of what accounts for enlarged brain. This may or

may not want to go in. But, basically, what they found was that the differences in brain volume is really due to differences in surface area, not cortical thickness, which does suggest some different developmental and genetic mechanisms. So, that is one we could include. I didn't know how important.

And then, there is a third study which is on air pollution. It is just a much more robust study on air pollution, linking high levels of exposure to traffic, pollution, during the prenatal period with a threefold increase in autism risk. So, when we get into why this happened, we might want to bring that up.

But I think that the two that have to do with immune function, if people agree, I would love to be able to add those, and I could just send the references with a sentence.

Dr. Birnbaum: I think that would be great.

Dr. Koroshetz: Yes, that is fine. That will be great.

Dr. Dawson: I will be concise, I promise.

So, are there other suggestions for this very detailed chapter?

Ms. Redwood: Walter, you had raised the issue about the recent studies have reinforced the overlap between ASD and GI disturbances.

Dr. Insel: Oh, yes.

Ms. Redwood: I agree that it seems a little bit out of place there. I know we were trying to figure out where to put some of the co-occurring issues. But I am wondering if that were sort of tied into the article that Geri just referenced by Ashwood, and then, also, with some of the microbiome and the immune system abnormalities, that it could possibly tie it in together more than the way it is right now, because it is just sort of a standalone statement without any

support.

Dr. Koroshetz: Okay. So, would it be okay, then, if we talk about the microglial paper in the new immune findings, and then bring in the piece about this gastrointestinal disturbance there? The question is which way to do it.

Ms. Redwood: Yes, and also, I don't know that there has been a whole lot of work on the microbiome and ASD. There was, I think, one study that was published, but it was in 2010, that looked at fecal microflora in ASD with controls, and found several abnormalities in different species. But that is the only thing that I know that has really looked at that issue in terms of GI flora and ASD in the last few years.

Dr. Koroshetz: Yes, I think that is going to be a gap area for sure.

Okay. So, I will move this GI thing up into new immune and tie it in with the new paper. I think that will fit well.

It will be less hanging.

Dr. Insel: I have a question about the term "co-occurring disorders," and this has come up before. It is not clear to me that we know these are co-occurring or whether they are actually part of a subtype of ASD. I want to make sure the language we use doesn't add to our confusion.

Dr. Dawson: The word "associated" I always think is less -- you know, because you could say "Autism is associated with impairments of social interaction," or something. So, I think "associated" seems like it could go either way. It could either be co-occurring or inherent.

Dr. Insel: Yes, that feels better to me. And Lyn's comment just now reinforces this for me, that we really may be talking about a form ASD in which the GI symptoms are absolutely a manifestation of the disorder and not a manifestation of a second disorder.

So, I don't think we know enough

yet to say that. But "associated" would be good.

Dr. Daniels: Tom? Are we on? Am I on?

I just wanted to say as a historical note, throughout the iterations of the current Strategic Plan, the previous Committee had chosen to use the wording "co-occurring conditions" through the Plan. So, I don't know if you want to stick with the wording that was in the Plan to make it so you are talking about the same thing, using the same term, or if you want to change that term.

Dr. Insel: Well, maybe we can take it back to the Committee in December and see where they are with this. I don't feel like we know enough to do one or the other. But, as I said, I just don't want to do something that causes people to think about this in a way that preempts the solution. Do you know what I mean? If what we are trying to do is get rid of the heterogeneity and get

clearer about the subgroups, this may be taking us away from that rather than towards it.

Ms. Redwood: Tom, this, also, whole section in the cross-cutting theme that we added on co-occurring conditions, that may be what Susan was referring to. It outlines in there that we really don't know enough about these to know if they are some primary aspect of autism or they are secondary features.

Dr. Insel: So, we maybe we don't want to make a change at this point, and it is something to address in 2013. I just raised it; as I look at this, it is the one thing that I worry might not be helpful. But, as I said, I don't know that we know enough to make a change yet.

Dr. Dawson: Are there other suggestions for this chapter?

(No response.)

If not, Susan, can you outline the

changes for the group that we have suggested so far?

Dr. Daniels: Yes. So, the changes that I have are, Geri, you mentioned a number of different references that you were interested in adding. Did you want to work with Walter to get those added in in the right places?

Dr. Dawson: Yes, absolutely. I will add the two on immune function, and I am drafting those as we speak. So, I will send those out right away.

Dr. Daniels: Good.

And on page 2 at the very bottom, change "and not necessarily genetic influences" to "as well as genetic influences".

For page 3, "co-occurring disorders," I believe that is under discussion, whether you want to keep "co-occurring disorders," talk about just those associated disorders or conditions or co-

occurring conditions.

And on page 4, Tom wanted to provide a couple of sentences to start out the gap section, talking about some of the transformative breakthroughs that have happened in the last 18 months.

And I believe that is all I have. So, unless anybody has anything else that they --

Dr. Dawson: Okay. So, could we get a temperature check on whether there will be folks that don't feel comfortable approving this chapter with these proposed changes to go forward to the December 18th meeting?

Ms. Redwood: Yes, I have a quick question. Susan, did you also include the information about the GI disturbances that Walter was going to draft?

Dr. Koroshetz: Yes, that is a paper that Geri has identified.

Ms. Redwood: Okay. All right. I just wasn't clear on when you running through

the notes about it.

Dr. Koroshetz: Yes, so, Geri, just send me that paper. I can deal with it.

Dr. Dawson: Okay. Will do.

So, Susan, would you like to call the motion?

Dr. Daniels: Okay. Do we have a motion on the floor to accept this chapter, Chapter 2, with the changes?

(Moved and seconded.)

All in favor?

(Chorus of ayes.)

Any opposed?

(No response.)

Any abstaining?

(No response.)

The motion carries, unanimous.

Dr. Dawson: Terrific. Okay.

So, let's move on to --

Ms. Singer: Before we go on to Chapter 3 -- this is Alison -- I was a member of this Subcommittee. I just wanted to thank

Walter for his leadership on this. I mean, this was a lot of material and a lot of diversity of opinion. I think we came out with a really nice product. So, I just wanted to thank him for his leadership on this chapter.

Dr. Koroshetz: It was easy. When you have a lot of material, it is easy.

(Laughter.)

Dr. Dawson: Yes, you did do a really nice job simplifying that, a huge amount of material.

So, now as we go into Chapter 3 and the lead begins to present this, we don't need, I don't think, to give quite as detailed of an overview as Walter did, although it was very eloquent and actually quite helpful. But I am worried that we will run out of time if we present that much detail, unless Tom disagrees.

I think what we can do is kind of focus on the discussion points and certainly

give some broader themes, if you wish. But I just worry we will run out of time if we provide that much detail.

So, I think if the lead could just give us a broad picture, but then focus on the discussion points that are raised on the drafts that were circulated, that would be helpful.

Ms. Redwood: Sure, Geri.

This is Lyn. I was over Chapter 3.

The people who worked on this predominantly were our external experts, Matt State, Craig Newschaffer, and Isaac Pessah. So, the work that you see here came predominantly from our external experts.

To go through some of the questions, it is going to be a little bit difficult. I went through the first round of edits, Geri and Tom, but when I opened this up the other day, I saw all of these new questions that were here. And unfortunately,

a lot of these are going to need to go back to the external experts, especially with regard to the references.

So, I sent an email out to Matt, Craig, and Isaac asking for their input on these comments. I think because of the holidays and the schedule, I have not heard back from them. I know that Matt is currently on sabbatical. So, the notes I have been getting from him are that he is not available. So, I will try to reach out to get some of these questions answered, but some of them I don't have answered at this point.

One of the first comments -- and I was just curious, Tom, where did these new comments come from? Was it from you or Geri or --

Dr. Insel: I think most of these are from me. I remember -- and I haven't looked at this in a couple of weeks -- in terms of the first piece of this, I had real concerns about how accessible it was to a

general reader. And I thought that, rather than listing a whole bunch of genes, it would be probably better to provide an overview, how to understand this enormous literature, because there have been scores, maybe more than scores, maybe hundreds of papers. It is impossible to try to get into this much detail at this stage.

Dr. Birnbaum: Tom, this is Linda.

I thought that one of the suggestions was that a table might help in here or bullets, and that would be really helpful.

Dr. Insel: Yes. I mean, the problem is there are well over 100 at this point genes that have been implicated, mostly in the last nine months. It is literally every issue of Science or Nature or Cell has a new report. I am just not sure how to summarize that with that kind of detail.

And I am not even sure at this point that the individual genes that are

listed in parentheses here are that important as a kind of overall perspective on what this is telling us about risk and resilience.

Ms. Redwood: And, Tom, I agree that it is very difficult to read. Would there be a way that you could offer some ways to sort of summarize it without actually including the individual genes?

Dr. Insel: I can go through this and make it a little more accessible. I mean, I think Matt has done a great job summarizing a huge literature. This is really difficult.

And as I note in one of these comments, there is no way you can keep up. I mean, even since this was written, there has been a Science paper out last week and another that is coming out next week. So, it is impossible to ever be entirely current.

But I think at the level we are looking at, which is at 30,000 feet, we can capture this in one paragraph and sort of get some of the take-home messages, which get lost

I think in this kind of a summary.

So, I would be happy to take a swing at that, but I don't know how to get it to the Committee. I mean, it will basically have to wait until the December IACC meeting. So, I will put it out there as an offer. If people want to do that, that is fine. If people feel like what we have here is important to include, that is fine, too. I would really leave it up to the group for guidance on this.

Ms. Redwood: I think if there were a way to summarize it, Tom, where it made more sense and looked at the different pathways, where it would be easier for even a parent to read, that would be really helpful.

Dr. Insel: Okay.

Ms. Redwood: Also, the very last thing that I think is sort of stated as a fact was really sort of a theory: “A substantial portion of ASD risk may be conferred by common variation acting in an additive fashion.” I

don't know that we actually know for sure that that is true. It is sort of based on selective meaning, and I don't know that there is support for that. So, I am questioning having that added, too, or if that is something that should be deleted.

So, if you would want to take a shot at that, I think the Committee would be very appreciative.

Dr. Insel: Okay.

Ms. Redwood: The next comments that we had, to revise this sentence to make it more readable, we can provide some language to explain that a little bit better. I think that was one of the additions from Isaac. So, I can get back with him on that and make it more readable.

There was also a question whether or not the Subcommittee agrees with this conclusion. I think the conclusion we are getting at, Tom, was that "New research has emphasized the substantial role for

environmental causes, potentially as large or larger than genetic heritability in the etiology of autism." Is that the comment you were referencing?

Dr. Insel: Yes. On this one, when I looked at those references, that wasn't what I got out of them. So, there are three references, 17 to 19. Only one of them is a new data paper, and that data paper I read quite differently.

Ms. Redwood: What if it was just 17? And again, this is portions of Isaac's. I can go back, but I think that was the main reference that he was making.

Dr. Insel: I'm sorry, the main reference was which one?

Ms. Redwood: The Hallmayer study, and you also had a recommendation here to move the U.S. twin study up to the beginning of the paragraph, which I think would also be a good idea, would make it read better.

Dr. Insel: Yes. And others may

have a different read on this. When I read the Hallmayer study, I don't think the data supported this conclusion. What it says is that there is a higher rate of autism in DZ twins than was at that time believed to exist in the general population or in sibs, so higher than the recurrent rate.

But, within six weeks or eight weeks of that publication, the Ozonoff paper came out with a new recurrent rate which was right on top of what Hallmayer was describing for his DZ twins. So, that kind of does away with his argument.

So, I ended up thinking that what Hallmayer basically showed was a higher rate in MZ twins than DZ twins and an equal rate in the DZ twins relative to other sibs.

Dr. Dawson: I read it a little differently.

Dr. Insel: Okay.

Dr. Dawson: So, I thought that it was a higher rate in the DZ twins and that the

take-home point was the shared prenatal environment that was accounting for the higher -- I mean, that is a hypothesis, but it was actually higher, quite a bit higher than what they found in the Ozonoff study. The point being that the DZ twins were sharing a prenatal environment and that this may account for the higher-than-expected rate.

Dr. Insel: Yes, I think my hitch there was I just don't believe the low rates in the non-twins kids, given that it is a pretty small sample. And when we have a much better study, the rate goes up to somewhere between 18.7 and 26.2.

Dr. Dawson: But those are not twins, though. Those are siblings that are --

Dr. Insel: Right. No, that is my point.

Dr. Dawson: So, they are just different. It is a very different sample. You know, I don't think you would expect the prevalence necessarily to be the same, if you

do think that the shared prenatal environment plays a role.

Dr. Insel: Right. But if you just start with the question of what is the recurrence rate, and is the recurrence in DZ twins higher than in non-twins, that is --

Dr. Dawson: Well, it was. I think it was 70 percent. In the Hallmayer study -- and I am doing this right off my head, but I think I have got this right -- which is 70 percent concordance in the identical twins and 40 percent concordance in the fraternal, but it was a high rate in the fraternal that was so surprising.

Dr. Insel: Yes.

Dr. Dawson: I mean, you have got 8 percent in siblings that aren't twins. And so the question, I mean, you could either say, well, it is a smaller study or you could say, well, they are twins and they share the prenatal environment, and that is pointing to the role of the environment.

Ms. Redwood: Geri, the other thing you could also say that would fall in line with this is that, oftentimes, twins also share the same postnatal environment. So, if you look at they are living in the same home, they are exposed to the same pollution, they are having the same diet in terms of breast milk or whatever the parents are feeding them, I think that falls in line, too, with the Baby Sibs study, and that siblings also share the same environment. So, I would be a little bit hesitant to just say it is prenatal environment only.

Dr. Dawson: Anyway, I guess there are sort of two ways to interpret it. One is that the larger sample is more reliable, but I would say that they are two very different studies. One is the study of twins, and the other is the study of siblings. And so, I wouldn't see them as comparable in terms of coming up with recurrence risk rates.

Ms. Redwood: What if we took out

that entire sentence there that starts with "This DZ twin concordance rate...."? Does that help? That was the one that you were questioning, Tom, with that reference.

Dr. Insel: Yes. Yes, I think if that sentence came out -- I think we need to say something about the twins study. I guess the problem has been how to interpret it, and this same discussion we are having is being held in the broader community as well. There is just a real struggle around not with the twin part of it, but with the sib/non-twin data, which doesn't match with other more recent data on what is the recurrence rate.

So, I don't know. I suppose --

Dr. Birnbaum: Rather than taking it out, Tom, can we just weaken the statements or make them think that it was a small study, or something?

Ms. Redwood: The twins study was actually the largest to date twin study.

Dr. Dawson: Right. And the

previous ones have been hugely smaller.

Ms. Redwood: Right.

Dr. Dawson: I mean, it is so much bigger than any of the twins studies that have been published before.

You know, I like the idea of softening it, that you could at least say, you know, that the higher-than-expected concordance rate among dizygotic twins suggests that shared early prenatal and postnatal environmental influences should be explored, or something like that, because it does raise --

Dr. Insel: Yes, but that is what I am struggling with. So, the next sentence which says, "This DZ twin concordance rate estimate was double a recent estimate of non-twin sibling recurrence rate.

Dr. Dawson: Well, yes, I wouldn't necessarily try to connect those two.

Ms. Redwood: That was the sentence we were going to delete.

Dr. Dawson: Yes.

Dr. Insel: Oh, okay. You can, although does that bother anybody else? Because, to me, it really does change the way you look at the DZ rate if it is about the same as what other people are finding as the general concurrence rate, at least in the Baby Sibs Project.

Dr. Dawson: But it isn't the same. It is larger in the dizygotic twins.

Dr. Insel: No, I don't think so. I looked it up, Geri. That is what is in that discussion, in the comment that says it was .21 for male twins and 26.2 percent for males in the Ozonoff study. So, actually, if anything, it tends to be lower.

Ms. Redwood: Weren't those a broader diagnostic criteria, Tom, in the Ozonoff study? I don't think that the criteria were the same. I think that was sort of a broader phenotype of autism. I will have to go back and look at it.

Dr. Dawson: Yes, I see the point you are making now, Tom. I hadn't actually read that particular discussion point.

So, you are saying that for male twins, rather than twins generally, if you look specifically at males, that their rates are closer --

Dr. Insel: Yes, exactly.

Dr. Dawson: Well, yes. So, that is a point well-taken.

Ms. Redwood: But there was also -- and I can't remember if this was in here previously or not -- there was a comment from the study that the heritability was sort of predicted to be 38 percent; whereas, the contribution from shared environment was 58 percent.

Dr. Dawson: What if we got away from the rates and basically just talked about that the Hallmayer twin study suggests that the role of the environment may be larger and that this deserves further study? Because

even the concordance rate for identical twins is lower than previous studies had found.

Dr. Insel: So, I am okay with that. The other option would be just to provide the numbers rather than just saying, as we have done here, "supports a large etiological for non-heritable, environmental, as well as heritable genetic causes". Why not provide the actual numbers for dizygotic, monozygotic, and then unrelated sibs from that study, and then note in the next sentence that the interpretation is complicated somewhat by more recent data on the recurrence rate in non-twin sibs from the Baby Sibs Project?

I think rather than drawing any conclusion, simply provide the numbers. Because you will see is that the DZ is about the MZ -- I'm sorry -- the MZ is about double the DZ. And then, the only question is how to interpret the DZ data with respect to non-twin sibs.

Dr. Dawson: Right. I guess the

only thing, I feel comfortable with that except for the sentence that states that the Baby Sibs data raises questions about the interpretation of the first one.

Dr. Insel: Because that is different enough, you know.

Dr. Dawson: Yes, they are just very different samples.

Dr. Insel: Right.

Dr. Dawson: And that is what is so interesting about them, right, the fact that one does have a shared prenatal environment and the other doesn't. And so, yes, I wouldn't want to say the Baby Sibs makes it likely that the first study was unreliable or something.

Ms. Redwood: I agree.

Dr. Dawson: I mean, I think the main thing is it is just raising lots of questions, right, that we need to have better answers to, and that we are just now beginning to have good data on recurrence rates.

Dr. Insel: Yes.

Dr. Dawson: And the fact that we are getting different recurrence rates, may prefer one sample versus the other, calls for more research in this area or something, to try to understand better.

Ms. Redwood: Geri, do you want to take a shot at drafting something along those lines that you just summarized?

Dr. Dawson: Well, I am curious, Linda, are you still on?

Dr. Birnbaum: I am. Sorry. I had to get off mute.

Dr. Dawson: Okay. What do you think about this?

Dr. Birnbaum: Well, I guess I kind of agreed more with you, Geri, than with Tom. These are very different populations, very different studies. I certainly read it as a focus on the prenatal exposures potentially really playing a role.

I think Tom is really

uncomfortable.

Dr. Insel: I am uncomfortable. Here is what is making me uncomfortable. I just went back to look at the Hallmayer paper to actually see what they did.

They didn't look at non-twin sibs. They looked at MZ and DZ twins, and they accepted the previous literature which said that the recurrence rate was 8 percent in sibs, which is, of course, much lower than the 21-percent rate that they found in the DZ twins. And therefore, you would conclude that shared prenatal environment is a very significant factor.

The problem with that is that the recurrence, the historical recurrence rate, was 40 percent of what we now know the recurrence rate to be, which is about 20 percent. And so, once you know what the actual recurrence rate is from the Ozonoff study, then their conclusion doesn't hold water any longer. And all this has happened

within the last 12 months or 18 months.

Dr. Dawson: Right, but you do notice -- I just pulled up the paper, too -- that the concordance for identical twins was .58 for 40 monozygotic pairs.

Dr. Insel: Right.

Dr. Dawson: That is pretty surprising, right?

Dr. Insel: Because it is low or high?

Dr. Dawson: Low compared to what our take-home had been before that.

Dr. Insel: Right. Yes. So, we could say that the rate in MZ twins was lower than previously described. But what I am concerned about here is the conclusion that the high rate in the DZ twins relative to the recurrence rates means that shared prenatal environment is a major factor here. Because I think anybody who reads this now with a broader knowledge of the literature would say, well, the recurrence rate is about what they

described for the DZ twins. Do you see my point?

Dr. Dawson: Yes. Though one thing to point out, too -- let's see -- for male twins, if you use ASD, the concordance rate is .36 for dizygotic pairs. That is twice the rate that you would see in the males in the Baby Sibs population.

Dr. Insel: Well, if you look at just male sibs, it is 26 --

Dr. Dawson: Not for ASD. That is for autism. If you look at the Baby Sibs paper, that is based on ASD, not autism. So, if you want to compare oranges to oranges, you have to look at ASD. So, it is about twice -- well, maybe not quite twice, but it is quite a bit larger for males at .36. It is a little farther down under results in the abstract.

Ms. Redwood: Well, Geri, I'm worried that we are taking up a lot of time.

Dr. Dawson: Okay. So, we will sort this one out. But I may I suggest, and

see what people think, that we do -- well, I guess the question is whether we make the statement that the Hallmayer paper suggests that we need to explore the role of the shared prenatal environment, as that could be influencing these concordance rates in twins.

And so, Tom, do you not feel comfortable with that statement?

Dr. Insel: Oh, I absolutely think it is true that we need to do that. I am just not comfortable with the idea that their data by itself supports that conclusion.

So, maybe what we can do is to find a way to word this. I think what would be best would be to actually provide the data to the extent that we can in the paragraph, actually give the numbers as part of an update, and let the reader herself or himself decide how to interpret this, because there is still very active disagreement about what the paper means.

I am also concerned we are taking

up too much time with this one point. But if where you want to end up is with a statement about the importance of shared environment, I am perfectly comfortable with that.

Dr. Dawson: Okay. So, the suggestion, then, would be that we give a detailed description of the concordance rates for autism and ASD for the two samples and then we don't try to link the Hallmayer paper as evidence to support shared prenatal influences, but we do make a statement generally at the end of the paragraph that says we need to continue to explore both genetic as well as shared environmental risk factors in prenatal shared environment, or something.

Does that sound reasonable?

Dr. Koroshetz: I think that is fine. If you look at the paper, I mean, their conclusions are just based on their data. I think those are fine. It is only when you get out and start comparing it to another study

where there were non-twins that you get into this mess.

Dr. Insel: I think that is fine. I think we are going to have to move on or we are going to get terribly behind here.

Who will try to craft that language here? Actually, I am willing to do it, and I can work with Lyn to try to get this following what you just said, if that is okay.

Dr. Dawson: Yes, that is fine. And I am also happy if you want to run it by me, too, or not, either way.

Dr. Insel: Right.

Ms. Redwood: I would like to have your input, too, Geri. That would be helpful.

Dr. Dawson: Okay.

Ms. Redwood: Okay. The next thing was whether or not to delete the sentence that has to do with cortical gene expressions that is known to emerge during fetal development. I think the comment was that it also is heavily influenced by

postnatal development. So, I would support deleting that particular sentence, the very last one on the first page.

The next comment is A(9) that deals with -- and, Tom, this must have been from you, and this is something you said previously -- with over 1,000 genes involved, can this be specific? And you highlighted autism, and then you have "delete". Could you share what your concerns were there?

Dr. Insel: Yes. So, I think what the text was saying was that, if we identify environmental chemicals that affect particular patterns of gene expression or particular pathways that genes are involved with, that may be a better way for us to go forward. I am not sure that is realistic.

Again, Linda is going to have a better sense of this. But it is getting to the point with literally hundreds of genes being implicated in autism and a thousand different genes in the synapse alone being

expressed, I am not sure that linking those environmental chemicals to any of the known signaling pathways is going to give you much traction. But I would defer to Linda as our environmental --

Dr. Birnbaum: I guess I am not sure I would agree, Tom. I think the issue is, to me, the point is that it is going to be effects on pathways or patterns that are going to turn out to be important, not a specific kink in any one given gene. It is going to be pathway effect.

So, I didn't have any problem with the way this sentence was worded, except that I would take out this parenthetical phrase that says, "specific congeners" because that is just going to confuse people about what we are talking about there.

Dr. Insel: It says, "Recent evidence has emerged...," blah, blah, blah. And so, is that evidence in those references 24 through --

Dr. Birnbaum: I believe so.

Dr. Insel: -- 29?

Ms. Singer: It would be helpful if you could give an example right in the text, not just a citation. But in other chapters where we have made statements like this, pretty sweeping statements, we have given an example.

Dr. Birnbaum: We could put in a statement with something like PCB 95.

Dr. Lawler: Right. I think the reference is Isaac's papers with the non-dioxin-like PCB.

Dr. Brinbaum: Yes, and I wouldn't even say that. I would just say, "Specific PCBs have been shown...." --

Dr. Lawler: Yes.

Dr. Birnbaum: -- and give an example. Cindy could do that. Yes.

Dr. Insel: Okay. I am fine with it.

Ms. Redwood: Your reference is

that is tracking a little bit different from the other exact list of references because there were three different people making edits to this? So, we are going to need to have to go over very carefully the references here, Tom.

I noticed that you mentioned the O'Roark study. That is listed, but the same one is listed twice. So, I am thinking that that second study you are referring to should be the second O'Roark reference.

Dr. Insel: Yes, I think the O'Roark one that I was mentioning just came out last Wednesday. So, I am not sure.

Ms. Redwood: Oh, then, it is not that.

Dr. Insel: Yes. That is what I mean. The field is moving so quickly in genetics and genomics that it is going to be difficult to ever stay current here, but we will do our best.

So, let's move on. I will

withdraw my comment there about the environmental factors and genetics.

Ms. Redwood: Okay. The next comment was, "Is there a reference that could be inserted for this statement?" I am sure there is. I will have to check with Isaac or Craig on that. I think that was supposed to be one of Craig's references, and I just don't know that it got inserted, Tom, but I will follow up on that.

Dr. Lawler: Yes, I think that was the folate paper that is described in the subsequent sentences.

Dr. Birnbaum: Yes, I just think it just needs some rewording.

Dr. Lawler: Yes. I don't think there is a separate reference. I think they are discussing that paper, sort of laying out the implications.

Ms. Redwood: Okay. The next question that you had was the concerns about advancing maternal and paternal age. You were

wanting to know whether or not this was a very strong finding because it had not been seen in other studies. Kong and Richenberg both were negative when the father's age was regressed out.

So, Linda or Cindy or Geri, or does anyone else have a comment on the strength of the paternal age association?

Dr. Birnbaum: I actually thought that was a pretty strong paper. Because isn't this the one -- I have to check what 14 is -- isn't this the one that showed the increase mutation as well that just came out a couple of months ago?

Dr. Koroshetz: Yes.

Dr. Birnbaum: Yes. So, I thought it was a pretty strong paper.

Dr. Insel: Which one, No. 14?

Dr. Birnbaum: Yes. But I think the maternal effect is more controversial. I don't know if maybe the way that sentence is worded conflates the two.

Dr. Insel: So, I think the biggest study done was the Kong paper, just out in Nature about eight weeks ago, from the Icelandic cohort. They did, in fact, find a maternal effect. But when they regressed that out against the paternal age, because obviously they are going to be closely-related, the entire thing was driven by the paternal-age effect.

That was found in all but one of the previous publications. I think the only person to report a maternal-age effect has been Peter Bearman, and that was a study which took a very different approach to this. It didn't have the same kind of dataset that Kong or Richenberg or any of the others have been able to work with.

So, I am not convinced at this point that the literature supports a maternal-age effect, but, again, there may be somebody on the call who knows this literature better.

Ms. Redwood: You know, it would

have been nice to have the experts on this call, too, so they could explain where some of this information was coming from.

Dr. Dawson: Yes, and I think it depends on whether you are looking at the genetic studies and have to do with de novo mutations as compared to epidemiological studies. I think the epidemiology studies tend to find a stronger effect for paternal age, but that there is some effect, weaker, for maternal age. But some genetic studies that are looking at de novo mutations point towards a paternal effect.

Dr. Koroshetz: There is a recent meta-analysis of the maternal age. I think there is some definite evidence that it is important, though.

Dr. Dawson: And those are epi studies, right?

Dr. Koroshetz: Yes.

Dr. Boyle: Yes, this is Coleen. I am back. I apologize for stepping off.

But the epidemiologic literature does suggest independent effects of both paternal and maternal.

Ms. Redwood: The thing I think we need to be careful about, though, is when you look at this long-term, say starting in the eighties, from what I was reading, there has only been about a 3-percent increase in a delay in childbirth, but it doesn't really explain the dramatic tenfold increase we are seeing in the numbers of children diagnosed with ASD. So, I think it is important, but it can't explain all of the increase.

Dr. Insel: Right. Lyn, do you want to add that in there?

Ms. Redwood: Sure. I mean, I think it is really important to look at, and I think it is important to look at in terms of, also, over age more environmental chemicals tend to accumulate in the body. So, that may be playing a role, too. I just simply don't know.

But I would be glad to draft something for that portion.

Dr. Insel: Well, the last sentence captures that, I think. It says the role environmental factors may play. So, it does get to that point.

Ms. Redwood: So, are we okay? Then, I guess the question is leaving in the reference to the maternal age.

Dr. Koroshetz: Yes, I am okay with it.

Dr. Dawson: Yes, I would think so, given the epi studies.

Ms. Redwood: Okay. The next comment here -- and, actually, I think this is the last one -- it was in reference to environmental factors in autism. And then, Tom, your comment is, "These references, only 19 provide new data," and "This reported mitochondrial function in 10 patients without evidence of environmental factors."

And I am not certain how to

respond to that. Again, this was Isaac's addition.

Dr. Insel: Yes.

Ms. Redwood: And the Belzoni paper is actually from 2010. So, I don't know if that was covered. I think that may have already been covered in our updates previously. So, that reference could be removed.

Dr. Insel: I guess I was coming down from a different perspective. I still see that, now that we have some 100-plus genes that have been discovered, what is so frustrating is that on the environmental side, we actually have nothing with those kinds of effect sizes to point to.

And so, I felt that starting this by saying that "New investigations have emphasized the absence of a role for environmental factors in etiology," I wish that were the case, but I think if there is anything that you would want to say based on

the last few years, it is that we have a much greater need to investigate environmental factors because we haven't been able to find the smoking gun, so to speak.

Dr. Birnbaum: Well, Tom, I think that would be a good point. I think one of the issues is that, when you find a specific genetic role associated with disease, you have a big effect in a small number of people, as opposed to environmental factors which will often have a much smaller effect but in many, many more people. So, for the population, it may have a bigger effect, as opposed to the individual.

So, that is part of the difficulty of finding the smoking gun in the environmental field because, if we knew who was susceptible to a given environmental stressor, we might be able to, in fact, find those very strong associations.

Anyway, I mean, I don't disagree, but I think your point about couching the

introduction to this is all the recent genetic data really has pointed up to the need that this is not explaining everything. It has pointed up the need for us to spend greater effort in trying to understand the range of environmental impacts and which things may be playing a role, in order that we can begin to avoid them.

Dr. Insel: Well, why not say that? Why not actually begin by saying that, "While there has been so much advance on the genetic side of this, what we still lack is more specific and" -- what is the right word? -- "more impactful set of factors from the environment that are contributing to autism."

Dr. Birnbaum: Yes, I think that would be great.

Dr. Boyle: This is Coleen.

One thing we could do is we could emphasize many studies or a number of studies that are going to come to fruition fairly soon. For example, our SEED study, which has

just completed the first five-year cycle, and there is data being analyzed, and it looks at environmental risk factors, broadly speaking, and other studies as well.

I mean, it has taken a while to develop that resource, but I think it will come to fruition soon.

Dr. Dawson: And also, what about some of the studies that now have been replicated. So, the folic acid study or the exposure to traffic pollution now, which I think there are three replications of that. So, if you are exposed during the prenatal period to very high levels of traffic pollution, I think the risk is threefold than if you are not.

So, I think there actually have been some pretty interesting findings over the last couple of years. And also, there is the questionable, but still interesting, effects of prematurity and certainly the infection during pregnancy. There was a paper that just

came out -- what? -- a couple of weeks ago that pointed to that one again. So, it is not like there hasn't been anything found.

Dr. Insel: Yes, except the infection paper was actually a negative finding. At least that was their conclusion. Though there was an odds ratio of two, they pointed out that, given the number of factors they had looked at, that could be simply a random event.

I guess I just thought this was an odd way to start this section, given that most of what we have been summarizing here in this section is what we have learned from studies of both genetic and environmental factors.

It seems to me that where you would want to start is to say, with a huge amount of traction on genetic studies, what we still lack is the ability to pinpoint high-impact environmental signals. And rather than starting the way here, which is to say what we have really learned is the important role for

environmental factors in etiology.

I think we ought to point to this as the most serious gap in the studies of risk factors and really focus on the need to get much more detail and much more traction on this topic.

Ms. Redwood: Tom, I agree. I think you are sort of spot-on with that; that does need to be changed. So, I think that would read better.

I can work on just that one introductory paragraph there, based on the comments that I have heard from everyone, and then ship that back out around with the other edits.

Dr. Insel: That is good.

Ms. Redwood: I also think that, in doing that, some of the gaps that we have is not collecting exposure questionnaires on all of these large studies, and that we may want to add that in here as well.

And then, again, in looking

through the public comment that we received for this meeting, there were several public comments that the parents are asking for vaccine research. That continues to be an area that is not really studied in terms of cumulative effects. We hear that from the public all the time, and I think that needs to be included in here somewhere.

Are there any other comments?

Dr. Koroshetz: Geri mentioned a paper coming out on air pollution. She suggested, you know, Question 2 would be, is it relevant to this chapter?

Dr. Dawson: I could certainly, like I am doing for the other two papers, provide one sentence and reference for that.

Ms. Redwood: That will be great.

Dr. Dawson: Okay. I will do that.

Ms. Redwood: Geri, could you also send those papers around?

Dr. Dawson: No, I have to wait

until -- I mean, it just went off embargo, but I have been looking and it is not on -- you know, I have to get it, and then I will for sure. I don't know if I can do it today, but within the next day or so for sure.

Ms. Redwood: That would be excellent.

Dr. Dawson: Okay. So, I am kind of getting aware of time. I was hoping we could do this one and wrap it up by more like 1:45 to keep on track and make sure we have time for all the questions. So, how are we doing in terms of discussing most of the points on this one?

Ms. Redwood: That was it, Geri.

Dr. Dawson: Okay.

Dr. Daniels: This is Susan.

On the last comments about collecting exposure questionnaires and vaccine research, was there any specific conclusion about what the Subcommittee wants to do with that?

Ms. Redwood: It wasn't vaccine questionnaires; it was exposure questionnaires, environmental exposure questionnaires.

Dr. Daniels: Exposure questionnaires and then vaccine research, and you mentioned those two things. But was there any specific action item?

Ms. Redwood: How does the Committee feel about that? We receive these public comments continuously. When you look at what has been done in terms of vaccine research, there has been one chemical and one vaccine that has been studied. There has not been any research into the entire schedule.

I think we hear from parents over and over again these stories of regression. Parents have been sort of leading the way, and a lot of the things that they have been telling us about autism for years in terms of regression, which we didn't think actually happened, and now we do have documented cases

of regression. So, I think that the gastrointestinal problems, a lot of the other problems that the parents have reported, I think this is something that deserves research, especially when there was something like 80 cases in a recent review of compensated cases in the Vaccine Injury Compensation Program that also had a diagnosis of autism that was precipitated by a vaccine injury.

Dr. Insel: Well, I guess the question is whether to single out any particular environmental factor. We have heard a lot about ultrasound, about soy products, about hypoxia at birth. In the public comments, there has just been a litany of potential factors.

My own sense about this is that we ought to continue to be open, and by saying there is a real need to study environmental factors across the whole range without listing any of those specific ones at this point.

Ms. Redwood: Susan, do you want to go through the edits? Or are there other comments from the Committee?

Dr. Daniels: If the Subcommittee doesn't have anything else to add, I will go through the list of edits.

My first one on page 1, that Tom, Lyn, and Geri will come up with some descriptive language about the concordance rates and the role of prenatal environment.

That at the bottom of page 1, the last sentence will be deleted about cortical gene expression.

On the second page, that Linda and Cindy will work with Lyn to give an example about PCBs or some other environmental factor to elaborate on the sentence there. And we will delete “specific congeners.”

In the second paragraph on page 2, Lyn and Cindy may need to do some rewording and make a specific reference to the folate paper.

On the last sentence or the second-to-last sentence on the second page, Lyn will do some work on that section to revise that opening sentence.

Did I miss something?

I didn't star this one. So, at the very beginning -- sorry -- going back to the top, Dr. Insel will go ahead and provide some updated information about new papers and take-home messages.

So, I think those are the changes that I heard. Are there any others that were missed?

Ms. Redwood: Susan, that last one that you mentioned, is that related to the first paragraph?

Dr. Daniels: Yes, that was the first paragraph.

Ms. Redwood: Okay.

Dr. Daniels: I just hadn't marked it properly on my copy here.

So, Tom will provide some language

about new papers.

Ms. Redwood: Okay. Thank you.

Dr. Daniels: So, I think that would be all, then, for this chapter.

Dr. Dawson: Okay. So, can we get a temperature check on whether there is general unanimity in terms of the support for these changes on Chapter 3?

Dr. Daniels: Sure.

Dr. Dawson: Is there anyone who does not feel comfortable with these changes?

(No response.)

Okay. Susan, do you want to call for the vote then?

Dr. Daniels: Do we have a motion on the floor to accept the chapter with the changes just described?

(Moved and seconded.)

All in favor?

(Chorus of ayes.)

Any opposed?

(No response.)

And are there any abstaining?

(No response.)

The motion carries to finalize Question 3 with these changes for submission to the full Committee.

Dr. Dawson: Great. Okay.

So, we are ready, then, to move on to Chapter 4. This is on treatment and interventions, which the lead will be --

Mr. Britton: Tiffany, are you here?

Dr. Farchione: Yes.

Mr. Britton: Yes?

Dr. Farchione: Yes.

Mr. Britton: I was wondering if Tiffany could summarize, if that is okay with you?

Dr. Batra: Yes, that is fine.

Mr. Britton: Okay. Great. And obviously, if it is okay with you, Tiffany. All right.

Dr. Farchione: Yes. I mean, I

actually would probably feel more comfortable if one of you guys decided to summarize because you really -- I mean, I realize that I integrated the document sort of together, but -- yes.

Mr. Britton: All right.

Dr. Batra: So, Noah, why don't I just summarize a few.

Mr. Britton: Sure.

Dr. Batra: And you can summarize what the gaps are, and then we can --

Mr. Britton: Sure.

Dr. Batra: -- have the discussion with the Committee. Okay?

Mr. Britton: That sounds fair. Great.

Dr. Batra: All right. So, just in the interest of the time, I will try to summarize very briefly.

So, Question 4 is the treatments and interventions section, what will help. So, we, basically, summarized the various

treatment options and interventions that have research supporting them over the last 18 months or so.

And we divided it into interventions based on different developmental stages or ages and different types of interventions. So, the first paragraph is on early behavioral intervention, which, again, a lot of resounding evidence supporting the benefits of early intervention and further identifying the core active ingredients to help that improvement.

The second paragraph is really looking at the interventions more for the school-age and adult individual. And again, a comment on the fact that there is very little interventions or supports looking at the older individual and the adult individual.

And then, the comments on some social skill interventions and some interesting CBT studies as well, some mindfulness studies.

The third paragraph was looking at medications as an intervention. And that is where there were a couple of comments that were made.

One was starting the third paragraph about the pharmacogenetics comment, that research is looking at genetic tendencies and targeting individuals' sort of responsiveness to various medications.

Tom, was that you or Geri who made that comment about leaving this out because it is relatively early?

Dr. Insel: Yes, Anshu, that was me. There is a lot going on with pharmacogenomics. I just wasn't sure that at this point we have enough to really talk about. I am not impressed that the stories that we have are really going to be clinically relevant. They are sort of scientifically interesting, but I wouldn't want to give people a sense in this update that this is a real breakthrough and that this will guide

the way we use medications. So, I probably would, until this is a little more mature, I would probably take it out.

Dr. Batra: I am fine with that. I thought perhaps we could put that in the gaps section.

Dr. Insel: Yes, yes.

Participant: That would be more appropriate.

Dr. Batra: Right. The early studies are looking at this and maybe we need to investigate it further.

Mr. Britton: Tom, it sounds like it really jibes well with what you suggested for the first paragraph under medications about the Precision Medicine Report. So, I am surprised -- I can understand that it is early, but I am just surprised to hear you be the one to say it should be removed. I am okay with moving to gaps, though. That is fine.

Dr. Insel: I am just responding

to I think this update should be on discoveries that really are breakthroughs or really kind of major findings. And this one is still pretty embryonic.

Mr. Britton: Yes. Okay.

Dr. Batra: Yes, I am fine with that, putting that in the gaps section.

And then, there was another comment about the paragraph about 12 medication trials launched, such as the arbaclofen study for Fragile X and whether it was phase 1 or phase 4. So, just some more clarification on that.

Dr. Dawson: So, that was information that I had provided. I think we could just make more general in its statement. I mean, it is a true statement, but I think that we could say something to the effect there of, you know, several studies or many studies have been launched addressing core domains of ASD or neurodevelopmental disorders associated with ASD, such as Fragile X, just

not get into the detail of phase 1 or phase 4.

The phase 4 study is the Memantine study by Forest. I think there is a second study -- I don't have it in front of me -- that is a repurposing study. But, if we want to be more general there, that might be better.

Dr. Batra: I am comfortable with that.

Dr. Insel: Geri, I have a question about that. I wasn't sure where the 12 trials came from. I just went to clinicaltrials.gov and looked at oxytocin and ASD, and there were 10 trials that are active, currently recruiting there, one or two that have just completed.

Twelve medication trials involved non-peptides, right? In that case, we are talking about mGluR5 and arbaclofen and those kinds of trials.

Dr. Farchione: IGF-1, pediatric IGF-1.

Dr. Insel: Okay. I am just trying to link that first part of the paragraph to the second part. So, should it say, "In addition, at least 10 trials of the pro-social neuropeptide oxytocin" or --

Dr. Dawson: No, I get what you are saying.

Dr. Insel: That is in addition to the 12.

Dr. Dawson: Yes, it doesn't make sense, you are right.

Dr. Farchione: Yes, because that makes it sound like 10 of those 12 are the oxytocin ones.

Dr. Dawson: Right. Right. So, why don't we just change the first one to many trials? That way, you don't get into what proportion. Because it is true that that particular one, that was just a slide that I had sent, remember, Tom.

Dr. Insel: Yes.

Dr. Dawson: And then, I think we

just took it off of that, and it didn't include the oxytocin trials on that particular slide.

Dr. Insel: But maybe that is okay then. Maybe we should leave it with the 12, because I think 12 is a very impressive number. I would have said it was much less than that. But I would just put "In addition" before the last sentence, so it is clear that those 10 are in addition to the 12 that you just mentioned, because, technically, oxytocin, you don't usually think of it as a medication because it is a peptide rather than a small-molecule.

Dr. Farchione: Yes, I like that idea. I think that makes it a lot more clear. And then, also, the idea of just taking out phase 1 through phase 4, because especially if this is in the general public, I am not sure that that even means that much to people.

Dr. Insel: Okay. Good.

Ms. Singer: So, can we go back to

the second paragraph on this page that says, "the systematic review of medications"? The way this first sentence is written, where it says, "concluded that there is moderate evidence to support efficacy, but strong evidence of side effects," it sounds like the evidence for the side effects is stronger than the events for efficacy, just the way that is written.

Dr. Dawson: And that is true.

Mr. Britton: Yes.

Dr. Dawson: That is what they conclude.

Mr. Britton: Yes. Right.

Ms. Singer: I think, then, we have to put in there that, despite this, it is the only FDA-approved drug.

Dr. Dawson: Yes, but --

Dr. Farchione: And the FDA wouldn't have approved it if we didn't think that the evidence of its effects outweighed, you know --

Ms. Singer: Well, I think we have to put it in there because I think, if you are reading this for the first time, you might think that there is some scant evidence of efficacy, but all this strong evidence of adverse side effects. But if you put in that the FDA approved it, then, I mean, that negates it. So, I think we should include both of those pieces of data.

Mr. Britton: But I don't know if that negates it. But, I mean, you can mention that it is an FDA-approved drug. I am fine with that.

Dr. Dawson: Yes. So, we could change it to "moderate evidence to support efficacy of" --

Ms. Singer: Why would you say "moderate evidence"? Why do you feel the evidence is moderate?

Dr. Dawson: That is literally what they -- these two terms are the terms that they used in their --

Dr. Farchione: I think that minimizes the benefit, especially when you have so few. You really have almost nothing out there. You just have the two medications that are FDA-approved. And, yes, they might not be miracle-workers and they might not touch the core symptoms, but they really are helpful in terms of decreasing the irritability and aggressive behaviors.

Ms. Singer: And in many cases they are miracle-workers.

Dr. Dawson: I think this is actually not --

Ms. Singer: It is also not new.

Dr. Dawson: No, wait, but it isn't the degree of impact on the individuals. It is how many studies have been conducted that support the efficacy. That is what this systematic -- sort of like when you review the studies on early intervention, the conclusion by systematic reviews is there is low evidence, believe it or not, for early

intervention, right? So, that doesn't mean that, of course, early intervention isn't effective. This is actually terminology that is just used by these systematic reviews that have to do with how many studies have been conducted that examined efficacy rather than how beneficial it might be for certain individuals.

Ms. Singer: Okay, so I am going to make the point, then, that I misunderstood the meaning of "systematic review", that it might also be confusing to other parents who are reading this document.

Dr. Farchione: And that is all I just wanted to say. Because I think that if this is a document that is aimed at the general public and not necessarily at academics, who might have some idea about technical terminology regarding level of evidence, then it is a little misleading.

Dr. Dawson: Fair enough.

Dr. Insel: Yes, that is a good

point.

Alison, how would you reword this? Because I think what we were trying to say was that there is real concern about adverse side effects here and they are so prevalent. And really, this was meant as a lead-in to the Scahill reference about the combined effect, which was how this paragraph originally got inserted.

So, is there a way to capture all of that, so that somebody reading this for the first time and trying to understand what is new would get a fair understanding of the data?

Ms. Singer: Well, I think what is confusing is the use of the word "moderate". I understand that it is in relation to the word "systematic," but I think the word "systematic" is what is unclear.

So, I think you could reword it to say that, "Despite FDA approval for Risperdal as a treatment for symptoms associated with

autism, there were studies this year that indicated evidence for adverse side effects." And then, go on to talk about the Scahill paper.

Ms. Singer: But not to write it in a way that makes it look like the evidence for the side effects is so much larger than the evidence for efficacy.

Dr. Farchione: Right. But I don't even think you have to take this fight because even the FDA study, you know, we list the side effects in the labeling. So, maybe if you just say that, "A review of medications," blah, blah, blah, "that there is evidence" -- leave out "moderate" -- and then, you just say, "However, these medications are not without side effects, including things such as sedation, weight gain," blah, blah, blah.

Ms. Singer: That is fine. That sounds fine with me.

Dr. Insel: Although there is

nothing new in that.

Dr. Farchione: No, that is not new.

Ms. Singer: Well, if it is not new, then we don't have to put it in.

Mr. Britton: But, Alison, the strong evidence is new, and that is why we are including it.

Ms. Singer: What is the strong evidence that is new?

Mr. Britton: Go ahead. Sorry.

Dr. Dawson: I am okay going either way because I always wonder about these systematic reviews and the way that they categorize things. So, this is one done by the Agency for Healthcare Research and Quality. This is the lead federal agency that is charged with looking over evidence of efficacy. They are the same ones that, like I said before, concluded that there was low, insufficient evidence to support even early intervention, and they also came out with two

reports this year on very little support for vocational interventions and, also, for adults and adolescents.

What they are trying to point out there is really the dearth of research that we have in the area of treatment. In other words, if you looked at heart disease or any other condition, and you saw there were like three randomized clinical trials or something and that is it, people would say, "Wow, we just don't have strong evidence yet."

And so, it is that kind of systematic review. And I am okay either way. They are significant reports, but I think that their interpretation and use of words can be somewhat confusing.

But these are pretty influential, big reports that do get a lot of attention and actually were mandated as part of the Combating Autism Act.

Ms. Singer: Well, I think it is fine to say the way it was suggested before,

that we need to continue to look at medications and side effects, and then talk about the Scahill study.

Mr. Britton: Well, we need to mention the fact that we have recently more evidence for the side effects. That is the new finding, and that is what is important to mention here.

Ms. Singer: Well, then, we need to state that in a way that indicates that this is still an FDA-approved medication and that the "moderate" is describing a type of review that I think is highly confusing, and we should --

Dr. Farchione: And again, maybe our view that this is not necessarily that new, because, again, all of the side effects are already on the label.

Mr. Britton: I guess to point out that we have stronger evidence for side effects than we did before. I am fine with pointing out it is FDA-approved. That I would

think would be obvious to a reader, but that is fair; we can include it. I have no complaint about that.

Ms. Redwood: I also think the strong evidence for adverse effects, it is really important to the parent community. This is the kind of information they are looking for. So, I think it is really important to include.

Mr. Britton: Thank you. I agree.

Dr. Insel: Tiffany, since you are the FDA official here, do you want to take a swipe at this sentence and figure out a way to work in the FDA approval?

Dr. Farchione: Sure.

Dr. Insel: Maybe we can move on.

Dr. Farchione: Okay.

Dr. Batra: Okay. So, where did we leave off? We have the last paragraph under medication, and then there is the paragraph about the co-occurring medical conditions, specifically the findings

regarding sleep and use of melatonin and efficacy, help with sleep onset as well as night awakening.

And I think there was a comment this is also in Question 2. Should we keep it in both places? I would vote to keep it in this section since it is a treatment or intervention that we do very commonly.

Mr. Britton: Yes, it seems to make more sense in the treatment section than in Question 2.

Dr. Batra: Yes. The No. 1 question I get is from parents; if kids aren't sleeping, parents aren't sleeping.

So, does anyone have any comments on that?

Dr. Insel: I think I was the one who wrote, "Does this need to be in both places?" And this was really meant as a question. I don't have a strong feeling about it either way.

And actually, I think that some

people may not read the entire update. So, there may be advantages to having a little bit of redundancy within the document.

Dr. Koroshetz: And I would take it out of Question 2, Tom, because it is basically treatment-related. We have other sleep biology issues in Question 3.

Dr. Insel: That is fine.

Dr. Batra: Okay. And then, the last paragraph is just looking at emerging interventions that are exciting. I think from a parent's standpoint they are new and different as opposed to the behavioral interventions and medications management that I think we all are well aware of.

But there are some nice studies looking at instrument-based intervention, music therapies, and a really nice study looking at rTMS and its improvement in executive functioning indices. Yes, I think that was it.

Noah, do you want to talk about

the gaps?

Mr. Britton: Sure.

Ms. Singer: Before you talk about the gaps, can we talk about one more thing that I think we have learned in the last 18 months? I am not sure why you chose not to put it in here.

But, over the last 18 months, we have learned that we can use imaging to validate treatment response, not only of medication, but also of behavioral interventions.

Dr. Batra: I am glad you brought that up, Alison. It was on my notes, actually, and I just forgot to mention that to the group. Thank you.

Mr. Britton: What sort of imaging are you referring to?

Ms. Singer: fMRI, EEG.

Mr. Britton: Oh, okay. Yes, yes, yes. Okay. I wasn't sure if there was a specific one. I think that is mentioned in --

Dr. Batra: Actually, I think I may have mentioned that in the gaps section last time.

Mr. Britton: Yes.

Dr. Batra: I agree. I think especially from looking at some of the studies that you and your group talked about in I think Question 2, you made mention of that. And I thought that was something we should do. But, again, I didn't know --

Ms. Singer: We didn't really do it in Chapter 2 because we decided it was more treatment-focused and it would be better in Chapter 4. So, I would like to see it now not be dropped from Chapter 4 and then appear nowhere, because I think it is something -- I mean, that is a huge thing we have been able to learn.

Dr. Batra: Yes, actually, it is, but do you mind sending that to us? Because I remember reading it.

Dr. Farchione: Yes, I think part

of the reason stuff like that didn't end up in here is because, as I was trying to integrate the documents that Noah and Anshu sent, I was really trying to focus specifically on treatment trials, intervention-type things, and not so much on kind of related but more peripheral things, in an effort to make it more concise.

So, if we did end up leaving some things out that you feel are important, hopefully, I made it concise enough that we have room to put it back in.

Dr. Dawson: This is Geri.

So, one of the studies that Alison is referring to, I think, is the study that we published this year on early intervention and electrophysiology. Is that one of the studies?

Ms. Singer: Also, Kevin Pelphrey has a study looking at pivotal response training --

Dr. Dawson: Yes, yes.

Ms. Singer: -- and very distinctive brain changes pre and post.

Dr. Dawson: Right.

Ms. Singer: So, there you have a biological signature of treatment response for a behavioral intervention. I think that is really not peripheral.

Dr. Dawson: Right. And I did actually include that. I added a sentence when I was working. If you look up under early behavioral intervention -- I didn't include Kevin's because it wasn't out at that point, but if you look under early behavioral intervention, about the fourth sentence down, it says, "Early intensive behavioral intervention was found to result in improvements of both social behavioral and neural responses to social stimulants." Now it is kind of buried in there, but it is there.

Dr. Insel: I guess I am behind the curve here. I only knew, Geri, about your

paper, which is listed in the first paragraph and Kevin's paper, but that is just a case report.

Dr. Dawson: Yes, Kevin's paper is awfully small.

Dr. Insel: Pivotal response training looking at --

Ms. Singer: Well, then, we should just talk about it as an emerging technique.

Dr. Dawson: Well, the study that we did was a pretty robust study in the sense that it was an RCT with enough -- but it is included. It says social behavior and neural responses.

Ms. Singer: The term "neural responses" didn't do it for me. I mean, I didn't even recognize that term "neural responses" as being measurement by imaging and it being a biological measure of treatment response. I don't think we have made enough of that.

Dr. Dawson: We could add a

sentence after that that says, "This is the first study to show that a behavioral intervention can result in a" --

Ms. Singer: "A measured change in brainwave activity and brain connectivity," something like that.

Dr. Insel: I think this is a really good point. I think that is a breakthrough. And I am not just saying that because Geri is on the phone.

(Laughter.)

I think that was more finalizing as a major finding. That is an example of the kind of work that we will need to see more of.

What I would suggest for the Pelphrey paper is that we insert it in the gap section, in the fourth paragraph which talks about outcome measures that can monitor changes in brain connectivity and/or activity and correlate those changes with behavioral and social therapies." So, using that as an example of the kind of the work that could be

done. Now that is using fMRI, not EEG, but it is a very powerful demonstration of what could happen and remains a gap in the field.

By the way, I think that paper is just out. I am not sure it was even -- maybe it was out earlier. But I thought it came out in the last few weeks.

Ms. Singer: I think it came out about two weeks ago. So, it is just out.

Dr. Insel: Okay.

Mr. Britton: Are we ready to go back?

Dr. Batra: Noah, why don't you talk about the gaps?

Mr. Britton: Sure.

So, before I do that, I just want to mention one thing at the very bottom of the first page of the "What's New" section. I didn't really get a chance to mention this.

Tom, you inserted this sentence. "An exciting example of this approach could should serve as a model for FDA-approved," et

cetera, et cetera.

About cystic fibrosis, I was just wondering if we can make that less specific because it seems very tangential, and you were the one who said you wanted to do the boulders, not the gravel. I think the previous sentence makes that clear, that we are interested in precise diagnostics.

I just don't want people thinking that this means that is where this research is going necessarily. I think it is too early to say that is true. And also, I don't want us to be thinking that treatments for cystic fibrosis are going to be similar to treatments that would be useful for autistic people.

Dr. Insel: When I re-read this, Noah, it felt like this was out of place somehow or didn't belong.

Mr. Britton: Okay.

Dr. Insel: So, why don't we just take that out?

Mr. Britton: Okay. Wonderful.

Thank you.

All right. So, for the gaps, we started with a paragraph summarizing the contributions of our four experts. The big thing about this is that everybody is saying we want more objective measures; we want more diverse samples; we want to make sure, basically, just that our research is done more scientifically, and that we have longer intervention studies, more sensitive measures.

The next paragraph is a large section on the impact of phenotypical differentiation amongst co-morbid conditions. One sentence that had a comment on it, which is a fair question to ask, is that it is possible that treatments for co-morbid conditions for autistic people need to be drastically different than treatments for the same conditions in the typical population. It said, "Clarify." I hope that what I am saying makes it clear and I hope everyone understands what I am saying with this. Yes? Do you at

least understand what I am trying to say here?

Dr. Dawson: I actually raised this question early on. I guess maybe it is just the way that it is worded because it sounds like that there is evidence now, right, that something came out this year that showed that, when you treat sleep with melatonin -- or I am just saying that as an example -- that you get this paradoxical effect.

So, I think maybe if we phrased it slightly differently, just the way you said it, that we don't know, that we need more research to determine whether interventions and treatments that would address similar conditions --

Mr. Britton: Yes.

Dr. Dawson: -- in this population have the same effects in the ASD population. I think that is a really legitimate point.

Mr. Britton: Okay. I have not seen published peer-reviewed evidence on this. I can look. But I have seen just talk from

people. So, that is where that idea comes from. So, yes, I can make that sound like we haven't found a paper on it recently.

Dr. Birnbaum: Noah, can we just remove that sentence?

Ms. Singer: I agree. I don't see why that needs to be there at all.

Dr. Farchione: I don't know that it makes sense to remove it altogether because that is something, I think, that concerns a lot of parents and a lot of clinicians. But I think it is probably important to point out, again, that we just don't have the evidence one way or the other.

Dr. Dawson: Yes, I think so, too. So, an example is anxiety. Having been in on a bunch of discussions about this recently, you know, there is this whole question about we try to use the same kinds of treatments that one would use with a person who has an anxiety disorder without autism. They aren't always necessarily effective. And maybe

anxiety in autism is something different.

Mr. Britton: Yes.

Dr. Dawson: I think this idea that there may not be parallelism in all of the symptoms, and that they may need to be tailored to the biology of a person's autism, I think it is an important idea.

Mr. Britton: Thank you, Geri.

Dr. Koroshetz: How about a sentence something like "It is important to understand whether the standard treatments for co-occurring conditions are as effective in individuals with autism as in typically-developed individuals."

Mr. Britton: That sounds fair.

Dr. Dawson: That sounds good.

Ms. Singer: I am good with that.

Mr. Britton: Is someone going to draft the language here or is this on me to write down what he just said.

Dr. Batra: Susan, will your office do that?

Dr. Daniels: Yes, our office will take care of it.

Dr. Dawson: All right. Thank you.

Mr. Britton: Thank you. Awesome.

Okay. So, the next paragraph is talking about alternatives to pharmacological treatments need further study. We have another section on rTMS, which I see this as a redundancy, but I am okay with leaving it in. I think it is important. And talking about figuring out what the active ingredients of behavioral interventions are and, also, making sure that they are studied in authentic environments, which is something that has definitely been understudied.

After that, we have more wording for improving objectivity in measures, talking about EEG, as we discussed before, Alison's point, and saying we need more studies on this.

The next paragraph on the bottom

of that page for the gaps is talking about phenotypical differences and saying what exactly are the core symptoms or characteristics of somebody who is going to benefit from a behavioral intervention as opposed to someone who is not and someone who may need a different type of intervention, and talking about how we have cognitive educational computer-based programs, and they have not been studied as well because we haven't done the phenotypical differentiation in our interventions to see why did this treatment work for this person and not for this other person.

Also, pointing out the need for inexpensive community-based interventions like yoga, exercise, acupuncture, just the fact that we need to do this stuff to find out whether it works. And we have some evidence of it on the bottom of the "What is new?" section, but we need more.

Shall I just continue? Or does

anyone have anything for the previous sections?

(No response.)

No? Okay.

The final paragraph is talking about something that I feel this is quite important. I am sure this will be controversial. So, I am open to hearing what people have to say about it.

"Interventions that have been commonly used and have little evidence need to be rigorously evaluated, so they can be disregarded if found ineffective." I think probably everyone is okay on that one.

And I brought out the point about iatrogenic effects of interventions. Pharmacological interventions, we know side effects, of course.

Behavioral interventions, side effects are just not being studied. I have seen it in person many times. There are side effects. Some of you have mentioned you have

seen this in person or heard talk about this from people doing interventions. The side effects of behavioral interventions, you know, increases on stress, decreasing unique talents, and decreasing quality of life, and the fact that we need to reconsider how we are weighing the effectiveness of an intervention because intervention studies are very mild: did this accomplish its goal of eliminating a behavior?

And then, I say, well, you know, if you cut off a thief's hand, he is not going to steal anymore, but was that really a worthwhile way of solving the problem? And really just the fact that we need to weigh the negatives and the positives together and find the net effects of an intervention as opposed to just doing the pure report of this decreased the behavior, and making sure that we have some measures to do this, to weigh these things and compare these things.

And the final thing I mention in

this paragraph is just that a lot of people are still not focusing on strength-based interventions and trying to get people to really hold onto the good qualities that they have before this intervention and not trying to delete their personalities in the process of changing these interventions and the fact that we are beginning to work on that.

I initially had a source for that from the Mottron paper that came out last year, which is what makes this a new gap area.

And the final sentence there is a discussion point, but I want to wait and see what reactions I have before we get there.

Anything from anybody? Or should I just continue?

Ms. Redwood: Noah, I had a question --

Mr. Britton: Sure. Sure.

Ms. Redwood: -- about the phrasing in that first sentence, "Interventions that are commonly used but have

little evidence and need to be rigorously evaluated, so they can be disregarded if found ineffective."

Mr. Britton: Yes. Yes.

Ms. Redwood: I think at the same time they also need to be used more universally if they are found effective.

And one of the things that I see --

Mr. Britton: Well, but -- sure, go ahead.

Ms. Redwood: -- is a really big gap area is that parents are desperate because there are so few drugs available and effective interventions. They are doing things, as you noted, without evidence.

Mr. Britton: Yes.

Ms. Redwood: I think that we really need to try to help parents make those types of decisions.

Mr. Britton: Yes.

Ms. Redwood: And I will give you

an example. This is something that I had some conversations with Walter about previously around microglial activation. It is something that continues to come up in the literature and to be well-documented, the recent study that you just mentioned, Geri, but we really don't know whether or not it is important to try to treat, keep the microglial from being activated, or is that a compensatory measure that actually I think we need to see work?

There are parents out there that are using treatments like high-dose non-steroidal anti-inflammatories and things for treating microglial activation. We have no research on that whatsoever. So, I really think things like that, that we need to delve into them so much more.

And what you are saying about these different comorbidities, that they may not respond in the same way, you know, a child that has GI problems with ASD, are they going to respond the same way as somebody with

ulcerative colitis? I do think those are important, but I think we really need to delve in more into some of these comorbidities, and it can really help improve family life, as Geri mentioned, if the child sleeps or not.

Mr. Britton: Right.

Ms. Redwood: So, that was my point. I think that is a gap area, is that we are not providing enough information for parents to make the decisions.

Mr. Britton: And I think that is what I was trying to say with this sentence. Originally, when I wrote this sentence, it was about chelation therapy, but someone took that out because it was just unnecessarily specific. As we all know, there are many interventions that fit in this category.

I guess, what would you propose changing the language to?

Ms. Redwood: I would have to sit and think about it.

Mr. Britton: Okay.

Ms. Redwood: I would definitely change that first sentence, though, about disregarded as being ineffective.

Mr. Britton: Well, what would you want it to say instead? You know, maybe not the specifics, but --

Ms. Redwood: That was it, that we need to provide information to determine whether or not these treatments are effective or ineffective. I think it is logical, if something is found not effective, that parents wouldn't want to follow it.

Mr. Britton: Okay.

Ms. Redwood: I don't know that that is really even necessary.

Mr. Britton: So, you want it to be more neutral? That is fair.

Ms. Redwood: Right. How many children with autism are on special diets? We don't have research in terms of that. We have one really small study that had a lot of problems with it.

Mr. Britton: We had a few, but, yes, that is something we can't conclusively determine right now. And I agree, we do need to investigate what that really does.

Ms. Singer: I think one way to look at this is to say that we could either try to make this paragraph more neutral or I think one strategy we have used in the past, when there was disagreement, is we put in one paragraph that indicated the opinion of one group and another paragraph that indicated the opinions of another group.

So, I think in this case the diversity of opinions is probably going to be some self-advocates have one point of view with regard to treatment and some parents have a diverse point, a different point of view with regard to treatment.

So, we could either try to get all of those views into one paragraph and make it very sort of middle-of-the-road and neutral or we could recognize this diversity of opinion

and write two paragraphs, one that starts off with some self-advocates believe this and some parents believe this.

I would be happy to work with Lyn on the parent paragraph.

Mr. Britton: I think you are talking about two different things. We were discussing, I think, the first sentence of this paragraph just now.

Ms. Singer: But I am broadening it to include the whole paragraph.

Mr. Britton: Right. I was just wondering if we were -- because they are different aspects of it. I am fine with leaving that first sentence more neutral and just saying we need more evidence for this; we need to investigate further commonly-done treatments, and leave it at that. That is fine.

Dr. Koroshetz: How about a suggestion that you go for some balance? So, you could say, as you have here, "so they can

be disregarded if found ineffective," "and widely disseminated if found to be effective."

Mr. Carey: Exactly.

Dr. Dawson: Yes, that sounds good.

Ms. Singer: That is fine.

Participant: I like the two.

Ms. Singer: That is good.

Dr. Carey: And, Noah, let me throw this question out at you. I mean, it sounds to me like she has thrown this paragraph in as balance to kind of the rest of the document. Is that accurate?

Mr. Britton: Well, I mean, I have thrown it in because I feel it is important, I guess. I suppose you could think of it that way.

Dr. Carey: Because I don't know if we need a second paragraph. I mean, it is tough putting this as kind of the last paragraph, I think, in some ways because it makes it much more of a conclusionary thing.

But I think there is a lot of other stuff in there saying we have all of these other things and here is this.

Mr. Britton: Yes.

Dr. Carey: But, I mean, I don't want to speak for you, but that is what I am feeling.

Mr. Britton: I see what you mean, and I think it does create a balance, I believe a balance in here. If you look at the rest of the language of this whole gap section, I think it should cover the parents' opinions pretty well.

Ms. Redwood: I was actually suggesting something in addition to that. That is that we also have a new paragraph that sort of addresses we know from several studies that parents of children with ASD are using a lot of complementary and alternative medicine approaches, you know, more than any other diseases that I know of, except for maybe cancer.

I could pull up those references. And yet, they are not really taking those things that they are using and subjecting them to rigorous science, and that is the gap that I am saying continues to exist.

Mr. Britton: Yes, and I agree. So, if we just changed the language of that first sentence to be more neutral, does that satisfy everyone?

Dr. Dawson: So, let me suggest more of a common-ground way of the issue that Alison was bringing up. Do we have two diversities of opinions about the sentence that talks about behavioral intervention and its unintentional effects on unique talents and things?

I actually think that is a really, really important concern. I would say that many people in the field of behavioral interventions -- I can't represent them -- but I think that most people would share that it is really important, and I wouldn't single out

behavioral. I would say, you know, "While many interventions report success, we always need to also study unintentional effects on unique talents and quality of life," that those always have to be weighed.

I wouldn't get into decreasing a target behavior because, actually, most behavioral interventions are focused on increasing rather than decreasing behaviors. So, they are developing social skills and developing language.

There are, of course, some that might be focused on something like reducing aggression, but for the large part, behavioral interventions primarily focus on increasing --

Mr. Britton: Right. Well, reduction or increasing being the same thing. I wasn't focusing so much on reduction, either, but --

Dr. Dawson: I mean, if we made more general and said, "While many interventions or treatments report success, it

is also important that research include assessment of any unintentional negative impact on stress levels, unique talents, and quality of life."

Mr. Britton: I think that is fair. The reason I included behavioral intervention, actually, while we were on our conference call with our experts, I forget who said it, but I was mentioning this point and she said, "Oh, well, yes, but this isn't really for behavioral intervention. This is just for pharmacological intervention." And I said, "Well, you know, I think that could be argued differently."

Dr. Dawson: And you know, the truth is, when you conduct an RCT on behavioral interventions and you have a data safety monitoring committee --

Mr. Britton: Yes.

Dr. Dawson: -- you do have to measure all of those things. And in fact, some of the studies are now measuring

cortisol, family stress, and a lot of other things to really look at the full picture.

Mr. Britton: Yes.

Dr. Dawson: So, I think if we say "behavioral," we could also say, while many interventions, both behavioral and --

Mr. Britton: Otherwise. Sure. I agree with that. Definitely include everything.

Dr. Dawson: I think it is a really good point to make sure that we are getting the broad picture.

Mr. Britton: Great.

Dr. Dawson: I am okay about that, but I don't know, Alison, if you think that just dilutes things too much, and how you would feel about that.

Ms. Singer: I think that there are some parents whose children are exceptionally impaired, and that they need to be represented in this document as well.

Dr. Dawson: Right.

Ms. Singer: I think if you are going to be including the point of view of some self-advocates -- and I agree that this is a legitimate point of view; I have heard it many times expressed by a diversity of self-advocates. So, I am not saying take it out.

But I have also heard the opposing viewpoint expressed by parents of very highly-impaired children who feel that this point of view really puts their children at significant risk for continuing to have self-injurious behaviors and aggressive behaviors that prevent them from being able to go to school and participating in the community. And I think that viewpoint needs to be included.

Dr. Dawson: Yes, I 100 percent agree with that. And I wouldn't want to have language that would take away from that point of view. So, if what I suggested implies that, then I would agree.

I guess I was just saying a middle ground is that, when we study any intervention

-- and I don't even think we have to say self-advocates have raised these concerns -- but, in general, when we study interventions, we need to look at both the positive and negative effects, whether we are talking about side effects of medications, whether we are talking about stress levels of a child who might be receiving too many hours and they are stressed out. You know, we always have to be looking at the full picture.

Ms. Singer: I think that is an important, but a different point.

Dr. Dawson: Yes, maybe it is a different point, I agree.

Mr. Britton: What is the thing that you would like us to add, Alison, as far as the language?

Ms. Singer: I think if you want to include this point that we need to worry about the unintended consequences of behavioral interventions and be as focused on loss of strength and loss of unique interests,

we also have to point out that there are some children for whom the critical nature of these interventions is such that, without them, they would not be able to participate in the community, they would not be able to go to school, they would not be able to participate really in any way.

I think, for those children, the value of the behavioral interventions, even the ones that decrease negative behaviors, including my daughter who likes to rip her skin off her arms, we work very hard to decrease that negative behavior. And I think that that has to be mentioned.

Again, I think this is an important point of view for a piece of the population. If you are going to mention it, then mention the other side of the population for whom these behavioral interventions are critical, and that the potential side effects of stifling her creativity or increasing her stress level is outweighed by the fact that

she is not ripping her skin off or banging her head against the wall and causing a concussion or a detached retina.

Mr. Britton: I think that is why I mentioned the net, not the gross, effects, is exactly for that reason.

Dr. Batra: Noah, the way it is written, it is a not specifically being without -- Alison, I absolutely agree with that because I think there is a multitude of families for whom, thank God, we have behavioral interventions and medications to help overcome the negative behaviors, so that the individual can actually access society, and the family can actually, you know, function fairly typically.

So, I don't know. Susan, do you want to jump in and maybe see if your folks can maybe generate something?

Dr. Daniels: If that is what the leads on this section would like us to do, we would be happy to try to reflect that in

there, along with whatever else you are providing.

It seems like Geri has provided some core language we could start with, and we could try to add that in.

Dr. Dawson: Yes. So, I think there are two ways to go on this. One is that we have sort of both perspectives reflected, the sort of self-advocate perspective that is reflected here and, then, the alternative perspective that Alison I think articulated well. Or we can make this a more sort of common-ground statement that is a little less -- you know, it is really focusing more on the idea that anytime we study these interventions that we really need to understand the wide range of effects, both positive and negative, and carefully document those and understand them, with the idea of minimizing in the long-run any negative impacts. I am actually comfortable with either. I think Alison's point is very important.

Dr. Carey: This is Matt.

Yes, I mean, I commented a little earlier, but I think Alison's of maybe her and maybe Lyn writing I think was a good one as well.

For me, I would probably try to frame it not so much as self-advocates and parents of more disabled children. I think it applies to everybody. Both sides actually apply to pretty much everybody. We need to kind of frame it in those two portions to make it work.

Dr. Batra: I mean, I really think that, Geri, what you said, I think that that is very appropriate. I mean, I don't think that we should be --

Dr. Farchione: I thought it was good, too.

Dr. Batra: -- writing a document that is sort of polarizing the issue. Because I think what I am hearing is everyone is agreeing, that, yes, while we are using

interventions to help individuals with ASD, that we have to keep in mind and be respectful of individual differences and individual strengths, as well as the potential side effects or benefits of that intervention.

And again, Geri, you said it so gracefully.

Dr. Dawson: I guess, Susan, would you want to just call for a vote on which strategy to take here?

Dr. Daniels: Well, it sounds like you could fit both of these ideas into that same sentence just by saying something about stressing the importance of having interventions to minimize the negative behaviors and symptoms, but also balancing that with looking at the various effects, both positive and negative. It seems like you might not need an entire paragraph to describe all that.

Dr. Batra: Right. And I just feel like it is something we are all agreeing

on. I don't think we need to waste any more words on it. I think it would be really a nice way to sort of end the document, you know, in a very positive manner.

Dr. Dawson: Well, I would be happy to try to draft something and run it by the leaders of this chapter, if that would be helpful.

Mr. Britton: That sounds good. Can we move on?

Ms. Redwood: This is Lyn.

Mr. Britton: Yes. Sorry.

Ms. Redwood: And I agree with both of you. I agree with you; I agree with Alison; I agree with Geri.

But I am saying something a little bit different than what you are saying in that sentence. My concern is that we have documented all of these idiological abnormalities in kids with autism. We have documented the immune disregulation and inflammation and oxidative stress and

microglial activation and GI problems and seizures. And we have not really looked at targeted treatments for those, or even understanding can they be treated or should they be treated.

And so, that is where I see a big gap. We have these documented like in Chapter 2, but we are not flowing over into the next logical step, which is what we do about them.

Mr. Britton: Lyn, are you talking about comorbidities, because we do mention that?

Ms. Redwood: I am talking about like immune disregulation. When I read your comorbidities here, I see that there is a focus on like anxiety and depression --

Mr. Britton: Yes.

Ms. Redwood: -- and psychiatric comorbidities, but not a focus on medical -- well, not that those aren't medical comorbidities, but on --

Mr. Britton: Where? Which part

are you referring to where you see that?

Ms. Redwood: Let's see --

Mr. Britton: Oh, okay, in the second paragraph. Okay. I mean, sure, we can include other stuff in that second paragraph, you know, anxiety, depression, GI problems, and acne, whatever else.

Ms. Redwood: I think immune problems we have documented over and over again that they exist and inflammation and oxidative stress and those types of things.

Mr. Britton: I guess we just didn't get into the list because it is very long. And so, we were hoping that just saying co-occurring conditions would be enough, and then we just gave a couple of examples.

Dr. Dawson: So, folks, I am a little concerned that we won't have any time for the last one.

Mr. Britton: Yes.

Dr. Dawson: So, maybe we should, I think we could certainly add a sentence like

that, Lyn, and you could help us craft that for the gaps.

Ms. Redwood: Okay. Yes.

Dr. Dawson: Susan, would you mind kind of going through our list now and seeing if we can get closure on this one?

Dr. Batra: Wait, I want to talk about --

Participant: Geri, I just wanted to make sure --

Dr. Dawson: Wait. Go ahead.

Dr. Batra: Geri, I wanted to make we commented on the last sentence that was highlighted.

Mr. Britton: Yes. Yes, me, too. So, this is something that I have a feeling is going to get shot down. I think it is important, so I will bring it up. But if it gets shot down, I understand.

So, I wrote this last sentence; I don't think it belongs at the end. It was originally not there. It was originally

elsewhere.

But just something that in an encyclopedia chapter I co-authored that will be out next year, and also in a journal paper that is in press, which I can send to everybody, I just mention the fact that it does seem that for social skills interventions one of the core mechanisms is putting similar people together who have similar interests and similar ways of thinking.

And I am referring to verbal individuals more broadly than I am referring to non-verbal individuals, although I would say that it probably applies there as well, but I have less evidence for that.

But, as far as all the social skills stuff, work that I have done, research I have done, interventions that I have been involved with, it seems that the core mechanism that is helping the people in the program is being put with similar people who get along with each other because they think

in similar ways.

And I wanted to mention that that is a thing that hasn't been studied. I think it is worth investigating. If you want me to change it to more neutral language, that is fine. I just want to make sure that someone looks into this.

Ms. Singer: So, this is, basically, arguing against the concept of mainstreaming?

Mr. Britton: No, not necessarily. It is saying that in a social skills group one of the things that seems to be most effective is putting people together who are similar and saying that, in social skills interventions, that may explain why there seem to be gains, regardless of the specifics of the intervention.

Dr. Dawson: Yes, but I think one issue there, Noah -- and I think it is a very interesting point -- there actually is some data that would suggest that having exposure

and time with typically-developing peers has a positive impact on overall social skills development.

In fact, in a major longitudinal study conducted by Marian Sigman, she found that the best predictor of positive outcome, long-term outcome, was time spent with typically-developing peers early on. And that ended up being sort of an argument for making sure that kids have time inclusive with --

Mr. Britton: Yes, I have heard things like that before. I disagree with their goals. I do think that is going to increase how typical someone is going to appear. I don't necessarily agree that it is going to improve their development in general. And I think that the measures they used are about trying to make someone appear more typical and not about improving their general quality of life.

So, again, like I said, this is a controversial position. I recognize that, and

I am fine with making it more generic, if necessary, but I do want to keep it in, if I can.

Dr. Insel: Noah, this is Tom.

Is there a way to frame this as a gap?

Mr. Britton: As what? Hello?

Dr. Insel: As a gap.

Mr. Britton: As a gap?

Dr. Insel: Yes.

Mr. Britton: Well, I mean, it is in the gap section. Well, I see what you are saying. So, yes, well, I guess what it comes down to is the gap being measures we are using in social skills groups. Are they measuring how typical someone starts to appear or are they measuring how happy they are afterwards and how comfortable with themselves they feel? I guess that is really the core issue I am getting to, unfortunately, and that is huge.

Dr. Insel: Okay. Yes, that is a different issue.

Mr. Britton: It is.

Dr. Insel: I think it is useful to know.

Mr. Britton: Right. Well, what I mean is that that underlies this finding which I am discussing, which hasn't been studied, I think, correctly. And, yes, there are data that would suggest the opposite being true as far as the usefulness of mainstreaming. But, again, I think their premises are flawed. And so, I don't know how to --

Dr. Dawson: Noah, what if we kind of worked this into the general statement that I am going to try to craft, with the idea that what you are raising again is a concern that, when we do interventions, we have to make sure that we are looking broadly at the impact and including happiness and quality of life as outcome measures, among other kinds of measures?

Mr. Britton: Yes. I think that is fair. I guess I want to make sure that

that doesn't end up being a statement that is so general as to mean nothing, because I do want to get these specific points in, and not necessarily this specific one, but the specific points I made in the rest of this paragraph I want to make sure are included somehow.

I guess all I am saying is just, can you send me the language that you draft before we get this out to the full Committee?

Dr. Dawson: Yes, absolutely.

Mr. Britton: Okay.

Dr. Dawson: I was going to try to draft something and send it to you and Anshu.

Mr. Britton: Okay. Yes, as long as we can approve this --

Ms. Singer: Can you send it to me as well, please?

Dr. Dawson: Yes, absolutely.

Dr. Insel: And, Geri, I would like to see it as well.

Dr. Insel: I like the theme of

this. And this is something that was not in earlier versions.

Mr. Britton: Right.

Dr. Insel: There is something new here.

Mr. Britton: Yes.

Dr. Insel: But I think we need to frame it in a way that is going to be most clear to people reading it because it is a little hard. When I first read it, I couldn't quite get my mind around what that meant, what this was. I think I now get this, but I would like to work with you on the wording of it.

Mr. Britton: So, yes, I will look forward to seeing what you and Geri draft for this. And then, I will send any replies to -- I will just reply to all.

Dr. Insel: Hopefully, it will be recognizable.

Mr. Britton: Hopefully.

Dr. Batra: In general, all the items that we have talked about, I think,

again, Geri and Tom, your creating sort of a nice, succinct statement that encompasses all that, I think that that would be a nice ending for this paragraph or statement, stating that at the end of the day, yes, we are using interventions, but keeping in mind the individual and the unique characteristics of the individual.

Again, I think that that is a very positive statement, you know, that is respectful. I would hope that would be received well by all.

Dr. Insel: So, it is three o'clock. I am mindful of the time here.

Susan, what do you recommend we do?

Dr. Daniels: We are fine to continue with whoever is on the call, as long as we still have a quorum. So, if you would like, I can go through the changes for this, we can vote on it, and then discuss 7. We will go over our time, but there is no legal

problem with that. It is just a matter of people's schedules.

Dr. Dawson: I have a 3:15 call, but --

Dr. Insel: Okay. So, I can stay on a bit longer. I think, for Geri and for me who worked on Question 7, it would be really helpful to get some feedback.

I think, Alison, were you on Question 7 as well?

Ms. Singer: Yes, I was.

Dr. Insel: So, maybe we could finish with this Question 4, and then take just a few minutes, before Geri has to go off to her next call, to get some feedback.

Dr. Daniels: Okay. So, you want to move to 7 before we vote on 4?

Mr. Britton: No.

Dr. Insel: No, let's finish 4.

Dr. Batra: No, let's vote on 4.

Dr. Daniels: Okay. So, do you want me to go through the changes?

Dr. Dawson: Yes, please.

Dr. Daniels: Okay. So, quickly, the first paragraph that Geri has offered has offered a sentence along the lines of "This is the first study to show a measured change in brain activity" for that first paragraph. That will be an addition.

On the last sentence on the first page, we are going to delete that.

On the second page, Tiffany is going to reword that first sentence of the first full paragraph about the systematic review to make it more understandable.

In the second paragraph, we are going to move this to the gap section, talking about pharmacogenomics and that as more of a gap area.

In the third full paragraph, to change the first sentence to take out the specific part about phase-1-to-phase-4 trials, to talk about at last 12 clinical trials and then add the words "in addition, at least 10

trials of the neuropeptide oxytocin". So, that would be changed.

And then, Walter suggested removing the open-label trial from the fourth paragraph, taking that out of Question 2. So, we would leave it here.

On the third page, we have language from Walter elaborating on co-occurring conditions. Is that what you have? Yes. Oh, okay, and working with Lyn to add some more information about other conditions, including oxidative stress. So, Lyn and Walter there.

And then, we have the Pelphrey paper being added to the fourth paragraph on page 3. And Alison may work with the Chairs on that.

And on the fourth page, we have a number of changes. Walter offered some language for the first sentence about evidence for these commonly-used interventions.

And Geri and Lyn will work with

the rest of the Subcommittee members who are interested in this area to revise the middle part of this, talking about behavior interventions, or, actually, any interventions and wanting to increase or support the positive effects without creating unintentional negative effects, reducing those.

And then, Noah will work on trying to take that last sentence and make it a little bit more general, to talk about measuring how these interventions are impacting the quality of life. And Geri was going to work on that as well with Noah.

Mr. Britton: Okay, yes. So, Geri, are you drafting that language and sending it to me?

Dr. Dawson: Yes. Will do.

Mr. Britton: Okay. Sure.

Dr. Daniels: So, I think that is all I have. Does that sound accurate to you?

Mr. Britton: Yes.

Dr. Dawson: Yes, it sounds right to me.

Dr. Daniels: Okay.

Dr. Batra: And, Noah, would you mind sending us that article that you were referring to?

Mr. Britton: I actually sent it to Geri and Tom, and I can send it on to everybody, sure.

Dr. Batra: Thank you.

Dr. Daniels: All right. So, then, we are ready to vote. Is there a motion on the floor to accept Chapter 4 with these changes?

Dr. Koroshetz: Yes.

Dr. Daniels: From Walter? Is there a second?

Mr. Robison: I will second it. John Robison.

(Moved and seconded.)

Dr. Daniels: Okay, John.

All in favor?

(Chorus of ayes.)

Any opposed?

(No response.)

Are there any abstaining?

(No response.)

So, that motion carries with a unanimous vote to accept this chapter with these changes.

Dr. Dawson: Okay. Well done, everyone. We have one more to go. Let's see if we can get Chapter 7 out.

Donna, I know you were the leader on this one. I also want to thank you for the tremendous amount of effort that you put into pulling together this information because it was very diverse and dense. So, thank you very much for all your work on that.

So, do you want to lead us through this one?

Dr. Kimbark: Sure. I am going to try to go as quickly as possible because I know we have a short amount of time here.

And you are welcome. I really appreciate working with everyone in our group.

I did want to say that we had a very diverse, different topics to discuss in the infrastructure group. So, I am just going to kind of focus down on the ones that had the questions on them, although if there are any questions from the whole Subcommittee on any of the other areas, we can go over those as well. But I thought at this point I think we should kind of look at the discussion points within the document itself.

So, most of the discussion points really zero-down onto biobanking and genetics sections of this infrastructure report.

The first question that came about was really about the brain banks that we have. We did discuss the 50 brains that were lost due to a freezer malfunction in June. But, then, we got into a little bit about the NIH and Neurobiobank that has been created.

What we really need to know is we

need a clear statement about how many brains are available to be added here. And we should probably go back to our experts on this.

What we have here from the discussion points is that this is probably evident; we have the Autism Tissue Program as well as the University of Maryland.

So, we actually need to go back to our experts in order to find out what that actual number is at this point.

Are there any questions about that?

Ms. Redwood: The only thing I would say is that, also, the NICHD brain and tissue bank with the University of Maryland has a donor registry. So, you might want to find out how many people they have in their registry as well, since you mentioned the ATP one.

Dr. Kimbark: Okay.

Dr. Kau: So, this is Alice Kau, NICHD. I can send you both information.

Dr. Kimbark: Oh, that is great. Thank you.

Ms. Redwood: And I guess the other question is, do we need to bring up the loss of the tissue in both sections?

Dr. Kimbark: I think we brought it up mainly to make it an imperative as far as the biolinking is concerned, because it was a huge loss of opportunity.

Ms. Redwood: Yes.

Ms. Singer: I mean, I would make that stronger. I would even say this is one area where we have regressed.

Dr. Kimbark: Yes.

Ms. Singer: Not only have we not advanced, not only are we not collecting enough brains, we have regressed.

Ms. Redwood: Yes, and I think also putting something in the gap area to prevent that from ever happening again --

Dr. Kimbark : That is actually a good idea. I was just thinking about that.

Ms. Redwood: Yes.

Ms. Singer: We have regressed and then talk about resolutions.

Ms. Redwood: Exactly, and what type of failproof measures can be put in place. I talked a little bit with Ron Zielke about that issue, and he may be able to help you with that.

Dr. Kimbark: Okay. And the next thing that came up kind of related to that is, what is the relationship with the neurobiobank and what Autism Speaks and the Simons Foundation are doing as far as brain banking is concerned. I don't know if we actually have to bring that up here or not.

What do people feel about that?

(No response.)

I am kind of thinking that it is kind of, I think it is a discussion point, but I don't think it is something that should be put in here when we are making a statement per se, unless is there a strong statement that we

need to make about the collaborations?

Dr. Insel: I think I put that in there. This is Tom.

Dr. Kimbark: Right.

Dr. Insel: We are the Autism Coordinating Committee.

Dr. Kimbark: Yes.

Dr. Insel: And as I read this, it sounded like the NIH has created a neurobiobank for NIH; Autism Speaks and Simons and others are creating their own brain banks. And one would wonder how all of this is being coordinated.

Dr. Kimbark: Okay. So, do we have an idea of how it is being coordinated?

Dr. Insel: I think it is, but --

Dr. Kimbark: I thought it was, too.

Dr. Insel: But it wasn't clear from the language. So, I think if it is, it ought to be stated. And if not, then --

Dr. Kimbark: Tom, I think it was

actually stated in an earlier version and it got cut out at some point.

Dr. Insel: Okay.

Dr. Kimbark: I could go back and check an earlier version.

Dr. Insel: I wasn't sure what the intent was, but it read to me as if everybody is doing their own thing and there is no coordination.

Dr. Kimbark: Okay. I will see if we have it in an earlier version. If I don't, I think I am going to talk to Geri about that in order to just get her take on it. Okay, Geri?

(No response.)

Dr. Insel: I think Geri had to step out.

Dr. Kimbark: Oh, yes, she stepped out at 3:15; that's right.

So, I will get in touch with her about that.

Dr. Insel: Great.

Dr. Kimbark: So, the next question was about the pluripotent stem cells, and we discussed this a little bit in Question 2. The pluripotent stem cells were brought up about taking fibroblasts and pressing them to pluripotent stem cells, and then inducing them into neurons, and so on.

So, I am not exactly sure if we need to keep this in here per se. I mean, I think that there is an emerging gap regarding methodology and getting enough of these types of cell lines, and so on. But I don't know if it is a status gap at this point.

So, shall we keep it or no?

Dr. Insel: I would say if the number is really 50 or anything under 5,000, I would take it out of here and put it into the gaps.

Dr. Kimbark: Okay. So, we will take it out and put it in the gaps.

Okay. That gets us into the genetics section. Our main big questions here

really are focused-in on the tables that we have. Do we want to keep the tables? I think they are nice and clean, and they state things very easily. It might be more difficult to state this in a paragraph. I think that it is always very difficult to understand stuff when it is in a paragraph form when you are putting out numbers. So, I would like to be able to keep both of these tables, if possible.

Dr. Lawler: This is Cindy Lawler. Linda Birnbaum had to get off the call.

But my sense is I think, if we keep these tables in here, we are really sort of committing to updating them each year and sort of potentially indicating whether sufficient progress was made in terms of when samples became available. And I am not sure --

Dr. Koroshetz: We have got to rewrite the Plan next year. So, I think we will make a decision at that time whether you want to have something like this updated each

year.

Ms. Singer: I don't understand, though, why you included some samples and not others. Like why didn't you include AGRE or the Simons Simplex? Why didn't you include those?

Dr. Kimbark: I think it was just what we were able to get the information from our experts, who were looking for the information and they pinged certain people, and this is the information that we got. But if this not complete, then I would suggest that we not put it in at all.

Dr. Lawler: Yes. This is Cindy again.

Because that was my other point: I am not sure if it is a comprehensive assessment. I think putting it like here with these specific numbers suggests that it is a complete assessment.

Dr. Kimbark: Well, I would suggest, then, that we take out the tables.

What we could do is fashion a couple of sentences that would actually use what we have here as an example and then also refer to AGRE and Simons.

Dr. Lawler: I would support that.

Dr. Kimbark: Okay.

Ms. Redwood: I agree. I think it is important information to have because it directly relates to some of our objectives --

Dr. Kimbark: Right.

Ms. Redwood: -- where we have actually specifically identified how many samples we want to collect. So, this will give us a way to know if we are actually meeting our objectives.

Ms. Singer: But I think this is a huge underestimate if you don't include the Simons Collection.

Ms. Redwood: I agree.

Dr. Lawler: The table suggest, the first table, Table X, newly-established. So, I don't know if that potentially suggests

why it is not complete. But even that --

Ms. Singer: But the Baby Siblings --

Dr. Lawler: It is not fully established. So, I think that is misleading as well.

Dr. Kimbark: Yes, I think if it is like that, I think that we shouldn't present it like this at all because I think it is misleading then. And we do have a sentence that is right above the Table X. It says about the Simons Foundation, but we don't have that data.

So, I think that that is problematic. I think that it would be much better for us to discuss this table, and especially Table X, in a sentence form now. I see your point as to how newly-established cohorts, especially in that collection, are being put together, and we are estimating availability for that. I think that would be a better idea.

Dr. Insel: Yes. This is Tom.

I would keep this simple. I think for both the brains and the DNA what we want is a status report. This is an update on infrastructure, and we should be able to say clearly how many brains are available. And if there is an expectation that there is going to be a bunch of DNA samples becoming available, that is fine as well. But I would provide the numbers, very specific numbers, but in a summary form.

The last sentence is fine. "The NIMH-funded Center for Collaborative Genomics distributes samples from 11,500 subjects, as of December 2012." That gives you a point in time.

And what we are trying to do is have these metrics on a regular basis, so we can say, if we are at 11,500 this year, we want to be at 14,000 next year and 18,000 the year after, something like that.

The same with brain tissue, we

should hold ourselves accountable for certain numbers, but I am afraid that the tables really confuse that issue because they are not clear exactly what the differences between those different studies and how this is being put together.

Dr. Kimbark: Okay. So, I think that what I will do, then, is remove the tables and write some strong summary sentences which will reflect what we have here in the tables, but will also give a broader view of what is being done as far as DNA collection is concerned.

Dr. Insel: Right. And you probably want to separate it into multiplex, simplex, and then clarify what is from probands and what is from other family members. And we will need to know what is available currently. It shows in the table what is being collected currently and is expected to be available in 2015.

Dr. Kimbark: Right, when it is

expected to be available.

Dr. Insel: Yes, that would be good.

Dr. Kimbark: Okay. So, everybody agrees on that, to make it a little bit, to make it much clearer, I think. Okay.

So, the other question was whether or not the 15,000 or so subjects, the last sentence in that area, are they actually ASD subjects and not including other people. So, I am not exactly certain. We would have to go back and find out and answer that question. I am assuming it was, but I might be wrong.

So, that is all the questions that we had as far as discussion points are concerned. Are there any other questions within the text of the Question 7 before I get to the gaps?

Dr. Boyle: Yes, I am sorry, I had my phone on mute. This is Coleen.

I did have one suggestion. This got cut when this question was edited. And

that is under the surveillance piece. So, one topic that has come up at the IACC, an important question, is why ASD prevalence has changed so dramatically over time. Since our last report, there has been considerable work that I think needs to be incorporated here.

CDC and Autism Speaks had a workshop to try to guide research on factors contributing to that increase. Since then -- that was in 2011 -- since then, there have been two, no, actually, three studies that have highlighted -- two that have highlighted the role of changes in identification and a third that has highlighted the importance or, actually, the limited importance of some perinatal risk factors on changes in ASD prevalence.

So, I mean, if people are okay with it, I would be happy to draft a couple of sentences, very brief, to include that within the context of the surveillance piece.

Dr. Kimbark: Right. I think that

that would be great. I think at one point, you are correct, that the Autism Speaks and CDC workshop did get cut out of here. But if you could draft something that was short and sweet, that would be great.

Dr. Boyle: Okay. Thanks.

Dr. Boyle: And I actually have to get off the phone in like two minutes. I don't know if we still have a quorum, but I just did want to let you know that I was leaving soon.

Dr. Kimbark: Okay. So, if there are no other questions regarding the actual discussions within the topic, I am going to go to the gaps.

I have written down here from discussions before that we want to put under brain and tissue bank how to do a backup system for the brain biobank.

I also think that it would be really, really necessary -- it just came to my mind now -- that we should talk to NDAR.

Is Dan Hall on the call?

Dr. Daniels: He is not a member of the Subcommittee, so he wouldn't be.

Dr. Kimbark: Oh, I'm sorry, that is correct. You are right. I'm sorry.

But Dan Hall, he was our expert; that's right.

I would like to go back to him and find out what kind of backup NDAR has as well because we are not only talking about backups as far as real backups for physical things, but also virtual backups for like NDAR and the genetics data storage, and so on. So, we have to talk about that and how they make sure that there are redundancies in the system. So, I think that that should be something we should find out if we have those redundancies, and if we don't, then put that in as a gap. Okay? Both physical and virtual.

And that is what I have for additions to the gaps. Are there any other additions that people would like to bring up?

(No response.)

Okay. That is, then, all that I have as far as this is concerned.

I am a little bit concerned about the references. We have to go through the references and make sure that they do jibe up with the rest of the document, because there is an awful lot of editing. And I am not sure if anybody did that or not. They were just kind of put at the back. So, we have to make sure that the references do match up.

Dr. Daniels: This is Susan.

That is something that OARC usually does.

Dr. Kimbark: Okay. That would be great because that kind of stuff just drives me nuts. Okay?

So, are there any other discussions or issues that anybody would like to talk about for infrastructure and surveillance?

(No response.)

Dr. Daniels: So, would you like me to go through the changes?

Dr. Kimbark: Yes, please.

Dr. Daniels: Okay. So, the first one on the first page in the biobanking section, Donna will receive some information from Alice about the NIH Neurobank.

In the next paragraph down, Donna will consult with Geri about a statement about coordination.

On the beginning of the second page, that first full sentence, that Donna will move that to the gaps section.

The next section on genetics, the tables will be removed and replaced with a couple of sentences. I think I have Donna doing most of this or consulting with other people.

The next one I have is toward the bottom of the page, that Donna will get information from experts about the ECG and SMD and the number of subjects.

On the next page in the surveillance section, Coleen is going to provide Donna with some language to add in about why prevalence has changed.

And on the next-to-the-last page, Donna is going to add some information about redundancy in both the systems for NDAR and the brain and tissue banking, consulting with experts, the NDAR folks and Dr. Zielke.

So, that was what I had. Does anyone else have anything else?

(No response.)

No? Are we ready to take to a vote?

Dr. Insel: Make a motion and take it to a vote.

Dr. Daniels: Okay. Is there a motion on the floor to accept this chapter with the mentioned changes?

(Moved and seconded.)

All in favor?

(Chorus of ayes.)

Any opposed?

(No response.)

Any abstaining?

(No response.)

With that, the motion carries to accept Chapter 7 with the aforementioned changes.

So, Geri is off the line. Is Tom still on?

Dr. Insel: I am here, yes.

Dr. Daniels: Okay. Do you have any --

Dr. Insel: I think this has been a really good process, a little bit long, obviously, but there is no simple way to do this to try to edit by phone.

I mainly wanted to congratulate everybody for doing a great job on these updates. There is an incredible amount of information to go through. I think with the experts or with your broad vision of what we needed, this is working out pretty well.

We will go through one more pass with these revisions, and then come back on December 18th and finalize this with the full IACC.

As questions come up in the meantime, we will use email to further do this as we need to.

Let me check and see if there are any last-minute questions before we adjourn the meeting.

Dr. Daniels: And then, Tom, I have some announcements when you are done with that.

Dr. Insel: Okay. Anything in the way of questions or comments?

Dr. Kimbark: I have a question, Tom.

This is Donna. Do you have any idea when you want to see these before the December 18th meeting?

Dr. Kimbark: Yes.

Dr. Insel: Susan is going to

cover that.

Dr. Daniels: Yes, I will cover that.

Dr. Kimbark: Okay. Never mind then.

Dr. Insel: Susan, go for it.

Dr. Daniels: Okay. So, just to tell you about next steps, each of the leads will be collecting the information they need for their respective chapters and integrating it to the best of their ability.

Would the leads find it helpful to receive a copy of the chapter with annotations where we need additions?

(Chorus of yeses.)

Okay. So, we will send that out. But you can feel free to start working on it before you receive it from us. But we will go ahead and annotate and send that out to the whole Subcommittee, so you can see where we have noted the changes are going to be placed within the language.

And after we receive everything -- so, we would like to receive everything back by this Friday, November 30th, to give us sufficient time to integrate all of those changes.

And the next step in this process normally is for OARC to go through and harmonize the formatting, language-smoothing in some places, and certainly consulting with those who have done the drafting, if there are any questions about that, to make it look like a uniform document. So, if there is no concern about that, we would carry on as we usually do when we are getting these documents together.

And so, on December 18th, you will see something that is integrated and all of the chapters will be together and, hopefully, somewhat formatted and smoothed-out for your consideration as a full Committee.

On December 18th, we will be meeting back as a full Committee to discuss

the full draft as it is and to see if there are any other changes before the Committee will have an opportunity to vote on it.

On December 18th, something that the public will be interested in knowing, we are planning a meeting; it is going to be a phone meeting with a webinar. But we will have public comment because it is a full Committee meeting, and we normally do have oral public comment at those meetings. But we will conduct those in a meeting room here at NIH in person. And so, The Federal Register notice and the website will have information about the location for that.

And so, anybody who wants to give oral public comment can come in person and we will webcast that, so all the Committee members and members of the public at home who are able to use their computers can see the oral commenters as they are talking. We will hand out the written comments as we normally do or we will send them by email.

So, it is a little bit unusual. We have never done that before, but we thought it was really important to make sure that the public has an opportunity to give oral comments, if they wish to do it that way. And certainly, we will continue to accept the written comments as they come in.

So, I think that that is everything. Do we have any other important pieces of business that need to be conducted?

(No response.)

So, I will be sending out the minutes by email to try to get those approved when we get them from the contractors.

So, that is all I have.

Dr. Kimbark: Can I ask one more question?

Dr. Daniels: Sure.

Dr. Kimbark: Does everybody on the Subcommittee have the emails for everybody else? I am not sure that I do.

Dr. Daniels: The email addresses

for --

Dr. Kimbark: Yes.

Dr. Daniels: -- the Subcommittee?

Dr. Kimbark: I know that I don't. I mean, I might somewhere in my huge inbox, but I don't know.

Dr. Daniels: So, when I send things out to the Subcommittee, I think that I normally put everybody on the email.

Dr. Kimbark: Okay.

Dr. Daniels: In fact, didn't the one that I sent out have everybody's email on it?

Dr. Kimbark: I think it did. I just wanted to know if there was like a formalized list that we could just have and save to our hard drive, rather than having to save an email per se.

Dr. Daniels: We could create a list and send it out at some point in the future, but I think we are going to work on the draft for right now.

Dr. Kimbark: Right, right. Go ahead. I mean, I just thought that if we had it, we could use it. But you don't have to do that right now.

Dr. Daniels: Certainly, but you can copy from my email out to the Subcommittee for the time-being. And then, we can provide a list. That is not a problem.

Tom? Are you ready to adjourn us, Tom?

Dr. Insel: Yes. Sorry, I just had to step away.

So, I think we are finished, and thanks again to everybody for hanging in there. It was a long meeting, but we got a lot done. And we will continue this by email.

Thanks, Susan.

Dr. Daniels: Thank you.

(Whereupon, the above-entitled matter was adjourned at 3:39 p.m.)