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INTERAGENCY AUTISM COORDINATING COMMITTEE

STRATEGIC PLAN UPDATE

Working Group 2 – Question 2 – How Can I Understand What is Happening?

Conference Call 3

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PROCEEDINGS:

DR. SUSAN DANIELS: Well good morning and welcome to our listening audience. And to the working group members for this conference call number three of the IACC Strategic Plan update working group question two, which is on the topic "How can I understand What is Happening?" about the underlying biology of ASD. We appreciate everyone being here.

And for those who are listening to the call, members of the public, you can find some materials online on the IACC website under the meetings tab and the subtab of working group. So, we'd like to start off today's call just going over the roles to see who's here. So, I will start that. Walter Koroshetz, are you here?

DR. WALTER KOROSHETZ: Yes, I'm here. Thanks.

DR. DANIELS: Thank you. Louis Reichardt?

DR. LOUIS REICHARDT: Yes, I'm here. Thanks.

DR. DANIELS: Thanks. And David Amaral? He may be joining us later. Jim Battey?

DR. JAMES BATTEY: I'm here.

DR. DANIELS: Thank you. Kevin Palphrey? Rob Ring is going to be joining us a little bit later. Nicole Williams?

DR. NICOLE WILLIAMS: I'm here.

DR. DANIELS: Thanks. Kasha Chawarska?

DR. KASHA CHAWARSKA: I'm here.

DR. DANIELS: Graeme Davis?

DR. GRAEME DAVIS: I'm here.

DR. DANIELS: Guoping Feng?

DR. GUOPING FENG: I'm here.

DR. DANIELS: Thanks. Heather Hazlett? Shafali Jeste?

DR. SHAFALI JESTE: I'm here.

DR. DANIELS: Eric Klann?

DR. ERIC KLANN: I'm here.

DR. DANIELS: Jamie McPartland.

DR. JAMIE MCPARTLAND: Here.

DR. DANIELS: Christine Nordhal?

DR. CHRISTINE NORDHAL: Here.

DR. DANIELS: Elizabeth Redcay and Flora Vaccarino? All right, so others if you happen to be on listen only and are waiting to join the call, please speak up once you're on the call and let us know that you're here. So, we appreciate having everyone here. And our working group chairs, Walter Koroshetz and Louis Reichardt have been also thinking about this since our last call. And we've been talking together about next steps.

Today, we're going to be assessing the chapter outline, which Walter passed around a more detailed outline. What I have for you is a list of topics that you all developed on the previous call and wanted to just make sure that we are capturing topics that you're going to want to cover in your chapter. And then Walter has organized the information into sections.

But, if you go to the list of topics, we have topics that are around the idea of looking at the biological basis of ASD. So, talking about molecular pathways, the molecular biology of conditions that are related to autism, some of the syndromic autisms -- developmental trajectory, sex

differences, neuro anatomy and circuitry, cognitive, sensory, motor systems and functions, biology across the lifespan and research on biology underlying abilities.

As opposed to just disability. Within that area are there other topics that you don't see on that list that you want to make sure get incorporated in the chapter?

DR. REICHARDT: I'm sorry, I have Walter's list up, which is what was sent to me. Can you tell me, reference what year is, I mean when it was sent?

DR. DANIELS: Sorry, I didn't understand the question.

DR. KOROSHETZ: I think the email just went out early this morning, right Sue?

DR. DANIELS: Yes, and I'm sorry that that went out so late. I've been out sick for a couple of weeks here. And so I wasn't able to get everything out earlier. I did send you an email this morning and all the materials are also up on the web. And that's fine if you haven't had a chance to look at it, I totally understand.

DR. KOROSHETZ: Lou, it came in at 10:02.

DR. DANIELS: So you have it in your email.

DR. REICHARDT: 10 or seven?

DR. KOROSHETZ: 10:02, two minutes after 10:00 this morning.

DR. REICHARDT: I have something. Is it the one that has the Walter and Louis have been missing in action on top?

DR. KOROSHETZ: No, it's a little earlier, eight minutes, that was.

DR. REICHARDT: For whatever reason, I don't have that. Sorry.

DR. KOROSHETZ: Okay, I'll send it to you.

DR. REICHARDT: No, I'm just, I'm sorry I mean I'm just…

DR. DANIELS: That's all right though.

DR. REICHARDT: Well, I mean I hope you're on the mend Susan, I should say.

DR. DANIELS: Thank you very much. Yes, I, in nine years I've never missed IACC calls and I missed two in the last couple of weeks. But I am feeling better and should be, you know, moving forward, trying to help everybody get work done on this strategic plan update.

So, on this list that I sent out, we have a number of topics that are things that you mentioned on your previous calls. So, I just provided you the list of some of the topics related to the underlying biology of ASD.

You also have some topics about the underlying biology of co-occurring conditions in ASD including epilepsy, enteric nervous system, and microbiome and GI disorders, immune metabolic conditions in autism and sleep disorders as some of the underlying co-occurring conditions. In addition, there were themes related to immigrating and collaborating across the continuum of ASD research.

And so you talked about increasing collaboration between federal and non-profit organizations. Creation of larger research teams and mechanisms for long-term funding of longitudinal studies. How to include people on the autism spectrum in planning and conducting research. Including individuals who are on the high needs end of the spectrum, and those who are minimally verbal in research.

Development of research outcome measures and quality of life outcome measures, the importance of replicability of research and research workforce needs, including specific areas of expertise such as engineering. And in the more detailed outline that Walter sent, he had some information about that as well.

But, as you look at this list, are there topics that you feel are very important that are not here that you want to make sure that we cover in our chapter? Is there anything that anyone feels that you'd like to add?

(No response.)

DR. DANIELS: So, and it's not necessary that you have to do this right on the call today, I just wanted to go over that with you.

And so, you have that list, you also have the outline that Walter shared, which is not on the web, we can put that on the web for folks if they're interested, it's a draft outline, much more detailed. In the written portion of this strategic plan update, we're looking for an update of 10 pages or less from the working group.

And so, you'll want to try to focus on major themes and major advances, and may not be able to mention everything in the field that, you know, you can't be totally comprehensive just because we need to make these chapters somewhat consistent. And we don't want to have chapter two being huge and all the others being a lot smaller.

So, we're going to set a bar at about 10 pages or so and you can see what you can do with that. Try to focus on what has been the most significant changes in the field in the last couple of years that are leading you toward your development of these new objectives for the strategic plan.

DR. DAVIS: So, I guess my comment would sort of reflect the email I sent out last night which

said the certain bullet points that you'd sent out this morning, I think accurately reflect kind of what the sessions have been about.

But, Walter's outline, which I sort of focused in on the section called what do we need, sort of jumps to a much greater systems level and a million or even human brain research focus. And I thought that kind of left over a lot of a lot of which in the bullet points that we have on our list.

DR. DANIELS: You thought, I'm sorry, you thought it did what compared to people?

DR. DAVIS: I thought it left over a lot of the sort of basic biology's, which is a lot of the kind of points on the list that you just highlighted on the web. Which I more or less completely agree with. But the document which has the outline and it sort of leaks beyond any of the earlier components of this list of things that the (unintelligible).

DR. DANIELS: I see. So maybe…

DR. KOROSHETZ: So Grae just said, just say which one's are you thinking of?

DR. DAVIS: Well, in the thing that you, is that Walter?

DR. KOROSHETZ: Yes, yes, this is Walter, yes.

DR. DAVIS: Yes, so I guess in your outline, you know, there's a lot of introductory materials on what we've achieved. And then there's this comment about what do we need, right? And it jumps to sort of greater knowledge through brain development, through longitudinal imaging of brain.

DR. KOROSHETZ: Yes, I got it. Which pieces are missing?

DR. DAVIS: Pardon me?

DR. KOROSHETZ: What parts are missing? And what's the emphasis? Or what, has the emphasis changed? Yes. Go ahead.

DR. DAVIS: The part that seems to me to be missing on the molecular pathways, the molecular biology of genetic conditions. Development and developmental trajectories. What I didn't see is the basic and molecular components of what we were talking about.

DR. KOROSHETZ: Okay, got you.

DR. DAVIS: Some of which are sort of just getting off the ground.

DR. KOROSHETZ: Got you.

DR. DANIELS: And it also might help just looking at the more detailed outline that Walter sent. You might want to reorder it from kind of more basic to some more clinical and applied type research. It might make it a little bit more logical for the leader. And so, then some of these topics that Graeme just mentioned maybe could go toward the beginning if they're more basic.

((Crosstalk))

DR. FENG: Hi, this is Guoping Feng. I want to add what do we need and what do we don't know. I think most of kinds of study of ways we are knowledge of (unintelligible) monogenic causes of ASD. And then many of them are probably polygenic and we don't know the genetic combinations. And we don't know actually how to study them in the animal models right now.

DR. REICHARDT: I don't disagree with any of that, I just would say that it's, I feel like some parts of the brain, some behaviors we understand better than others. In particular, I'd say we

simply don't know enough how to evaluate function in the forebrain for example.

DR. FENG: Yes, that's also very true.

DR. KOROSHETZ: So Sue you know, the initial strategic plan, it did have those two sections, what do we know and what do we need. So I thought that was worthwhile doing, I appreciate Graeme's point that we don't want to overemphasize what we know. But in terms of that piece, as it was mentioned, most of what we know comes from the monogenic forms. And then the brain imaging stuff in people has given us some clues.

DR. REICHARDT: But they've been correlational cues, that's got a lot of challenges, you know.

DR. BATTEY: Yes. So, one of the big challenges I think is to distinguish distinct correlation and causation.

DR. REICHARDT: Yes. I think that's, I agree completely with that, yes.

DR. KOROSHETZ: And in terms of explaining the core features of ASD, you know, I basically listed that we have more information about what they are but not really how to explain them. Anybody want to add in any points there that could, potentially if a parent was reading this, give some glimpse into what evidence there is for the biological basis of these different difficulties that the patients experience?

(No response.)

I mean I think we're still pretty much in the dark. Into some stuff, in terms of, like Jim, in terms of language, I don't know if people buy it, but changes in, you know, connect in language areas. Are those worth highlighting or not?

DR. JESTE: I think we could add some information there about correlations we've seen in

imaging studies that underlies some of these deficits. There's some connectivity differences that are correlated with social interaction or language ability or things like that that we could highlight a little bit more.

DR. REICHARDT: There's some beautiful model, animal model studies that, you know, for issues like repetitive behaviors, which is certainly an issue, or at least would be things that one would ideally like to extend to humans. And I think, you know, comparison or extension of Cosby's study done on animals to humans, whether by profiling, a connection assessment, is just extremely important. They're pretty proud of it at this point.

DR. KOROSHETZ: Okay.

DR. DAVIS: So, can I pose a question to everybody perhaps. Which is that I think everyone struggles with this notion of correlation versus causality. And obviously causality is what one would really like to have a handle on. What would be the way forward there? One thing to put out there that we need that, and the other thing is to provide some idea about how one would achieve that. I'm actually sitting here thinking about it and I don't know.

DR. KOROSHETZ: Well, we have to have an intervention. I think (unintelligible) you really know it, it's causal.

DR. JESTE: Well I would say also, I mean in the animal studies you can manipulate the system to look at causation I think a little more easily. But then you're stuck with, you know, very specific preclinical models that are either monogenic disorders or other, you know, other nervous system hits. I think that in humans the way to really disentangle some of this is (unintelligible) as early as possible and development.

And I know that that was one of the points. But I would say, you know, someone is kind of actively involved with the early infancy work and I know Kasha's on the call too. I mean, I think it's very challenging to perform those studies in a way that's powered and effective to really understand kind of mechanisms that underlie, you know, atypical development.

But what we need is really large studies that combine neuro imaging with genetics with behavior, right, to really, you know, study these infants before they develop symptoms of autism, before they develop symptoms of cognitive impairment. And to really kind of understand pathways to that. And so I think that, you know, it doesn't… I think to look earlier in development will help us really start thinking about causation.

And I think that, you know, the idea of kind of integrating these different modalities of investigation I think can actually be done really, probably more cleanly in infancy, right? Because we don't have already the core morbidities that we're seeing in adults and adolescents with autism, where we're doing most of our imaging studies, right?

So, we can really start understanding these fundamental mechanisms like destruction of some connectivity and other processes. So, I would say that, you know, to me, you know, as a clinician who studies and takes care of older children with autism as well. I think that to really understand the biology, we need better studies in very, very early developmental periods.

DR. CHAWARSKA: And just to add to what Shafali said, I would say that implanting development studies during this very early stages of development, even during program…

DR. JESTE: Right, right.

DR. CHAWARSKA: … is tremendously informative in terms of the mechanisms.

DR. JESTE: Because I think, you know, in the imaging work, and I say imaging loosely, I mean electro physiology and on tracking, and MRI and everything else in imaging genetics, you know, we're stuck with this major problem of heterogeneity. Which is, you know, fundamentals of autism. And I think that one of the biggest challenges in the imaging field is that most of the studies are done in certain pockets of the spectrum, right?

So, we're studying a lot of higher functioning, older individuals because of feasibility. And we're making conclusions and we're correlating behaviors to imaging. But I would say that, you know, and I don't mean to sound cynical, but I think that I don't know that actually we've really answered fundamental questions about the biology of autism through studies like that. I think that we've started to get glimpses of where circuits may be disrupted.

But I think we really need to have more creative ways to think about the heterogeneity and why certain outcomes emerge and develop. And so I think that to do that, again we need large samples, but we need representative samples too. And I think looking earlier in development will help with some of that as well.

DR. CHAWARSKA: And also, again capitalizing on methods that are immutable for studies with individuals across the age range and also intellectual ability. And there's some methods like eye-tracking for instance, which is tremendously versatile and can be used starting in very early development newborns.

And really that does not require any manual responses or verbals infractions. So, thinking about development of brother portfolios, and models like that would be tremendously important.

DR. JESTE: Yes, I completely agree with all of that. I would add to the idea of starting earlier in development that we also need to look at the heterogeneity of autism and look at subgroups of autism. Because we're not going find causation across the entire group of individuals with autism, we have to look at pockets of subgroups.

So, for example, in the what we know, brain overgrowth during a specific period of development, I think that there's several studies now that show that that's occurring in about 15% of kids. And so we need these large sample sizes so that we can satisfy by these sub, look for causation and look early in development in subgroups instead of the whole group.

((Crosstalk))

DR. REICHARDT: I would just say, I think that all the proposed studies should include at least some genetic to make sense of it, you know.

DR. FENG: I cannot agree more about the subgroups. I think, you know, it groups them together as an autism, as one entity to study actually, detrimental to this field. Actually it's really making study much, progress and much (unintelligible). And I think understanding subgroup then really understanding where biology of the underlying subgroup will the path for us to really understand autism.

DR. JESTE: And I agree. And I think where it gets complicated, I mean I think the monogenic disorders have been extremely enlightening, right? Because we do, in those groups, understand, you know, at some level, a sort of fundamental mechanisms of disruptive brain development. And then we can sort of track that through preclinical models to patients.

But, you know, even within those syndromes, like TSC, I mean we see heterogeneity there as well, right, we see differences in outcomes

despite very similar clinical profiles and genetic profiles and other things. And so I think, you know, maybe there's, you know, and I know there's been proposals coming out now looking at, you know, polygenic risk and other things in these even monogenic syndromes.

But I think, you know, it's a struggle to say we need to link everything back to genetics. Because I think we do, I think that's a big reason for the heterogeneity. But from a prognostic standpoint, a lot of heterogeneity is going to come from differences in common variation and again polygenic risk and other things.

And so how do you approach that problem, right? And it has to be done through very large studies, but ones that then can link the kind of insights we gain from that heterogeneity and genetics straight to brain. I think what we do right now is we have a lot of really rich studies in genetics that are, you know, extremely informative.

But then we link, we try to then create subgroups based on really fairly crude behavioral measures. And we kind of miss that whole middle piece, which I think is what we're all talking about today. But I think it'd probably shed really nice light on some of the pathways to those, that variability.

So, really doing like imaging genetics, but in a way that's more robust and can help us understand kind of mechanisms of heterogeneity I think will be a really key, you know, key priority for us hopefully over the next few years.

DR. DAVIS: So, I could not agree more. I think that's a wonderful statement about it. And I, just to follow up a little bit more, I do think that that made, you know, this polygenic or kind of inherent background modification, I think is discoverable.

And perhaps even understandable to some degree if it were tackled as a problem. Even at the genetic and molecular level. And that's sort of where we hit upon some ideas relevant to system biological approaches here. Which it could be very powerful.

DR. KOROSHETZ: Are there any precedence in other disease?

((Crosstalk))

DR. DAVIS: Intervening piece, which I think is also important. Which is that it may not all be structural in the circuitry, but also functional in the circuitry. And therefore, difficult to observe in a map of the nervous system.

DR. REICHARDT: That's absolutely right and in fact there's certainly examples of that for example, the Roswell setup papers on repetitive behaviors. It was in cell a couple of years ago. It was not structural it was functional.

DR. KOROSHETZ: So, Graeme, in terms of the molecular side of things in my number under four, what do we need. That was kind of where I was putting that. Now, so what type of things would you add in there? It was…

DR. DAVIS: Let me go to number four here. So…

DR. KOROSHETZ: Understanding the neuro effects of genes implicated in ASD.

DR. DAVIS: So, you know, what I might do is suggest that we have gained this incredible foundation based on the monogenic and rare variances of higher penetrants. And that's a real highlight. The emerging challenge that that has given us is to understand how any individual with one of these mutations might present across a wide spectrum of phenotype in a human patient. And that would be true for virtually all monogenic diseases.

And so, that really becomes a system of biological questions which is the interaction of any disease-causing gene with the genome of individuals that creates the phenotypes of the patient. And I think with the kind of systems, biological approaches of large datasets, the power of sequencing and even the power of very large abilities to record populations of neurons as they function.

This is potentially a swallow-able question. But, you know, and they bring us to entirely new avenues thinking about how to treat the disorder. Which would be treating the, you know, pathways that are perhaps commonly manipulated. But downstream of the individual gene, which as yet, don't make any sense of the common kind of pathway towards phenotypes.

DR. REICHARDT: I would say, Walter I would just say under number four I think the need for quite detailed studies on many levels on postmortem human materials is received through tragedy or whatever is very important. I mean, it's not just IPS cells.

DR. KOROSHETZ: Right.

DR. DAVIS: But I would even go so far as to say that there are some, you know, IPS cells even in the sort of model systems world where fundamental pieces of biophysics could be dissected out in this clinic way. It is also important.

DR. KOROSHETZ: Right. Okay, so I think I got that.

DR. BATTEY: Are those IPS cells been differentiating as the neurons? Or are they just IPS cells?

DR. DAVIS: That's a good question. And I, you know, in truth I'm not so sure that we have the ability in the IPS cells that are differentiating

the neurons to really do the right kind of (unintelligible). Or whether they're going to represent, you know, neurons of these different types. But it would be something to continue pushing forward because there is potential power in there.

DR. KOROSHETZ: Right. And also I've been impressed by some of the work on the organoid, brain organoids that's being generated from neuro precursor cells. Some really interesting almost cortical formation, where you can actually study migration and differentiation cells that form cortex.

DR. REICHARDT: Yes, I guess, I mean I guess the other supplement of that is in fact, there's been great progress. And actually integrating human net neural cells into model organisms brains. So, like for EmTech, I mean which in principle gives you much more differentiated in specific phenotypes.

((Crosstalk))

DR. DAVIS: So, I guess I would add one more specific thing in there which is that the power crisper, rapidly enabling in the Malian system, the power of combinatorial genetics. Which before was prohibitable expensive. And so there is the possibility of exploring these kind of genetic interactions and polygenic processes that new doors are being opened simply because it's possible to manipulate (unintelligible).

DR. KOROSHETZ: So, I had in the two, the emphasis on the postmortem tissue.

DR. REICHARDT: Yes, I would agree to that. But I would say particularly postmortem tissue from young individuals. Which I realize is especially sad to get. And there, the circuit, I think it's just very important to trace impact of genetic mutations, you know, immune challenge, whatever, down to specific cells and specific circuits.

I mean we know that the behavior reflects function of very - quite specific circuits. And so it has to go much more in detail. And what we've, you can't emphasize the need for getting down to the cell and even synapse level.

DR. KOROSHETZ: Okay. If we just go, so back again, Sue, are you still on the line?

DR. DANIELS: Yes, I'm still here. I'm just listening to your…

DR. KOROSHETZ: I guess my question is in terms of how it looks. So, do you see any issues with going back to the what do we know, what do we need?

DR. DANIELS: No. I think that that structural probably helped you all for the meeting.

DR. KOROSHETZ: And then go to barriers and policy issues.

DR. DANIELS: Yes, I think that that will probably be fine.

DR. KOROSHETZ: Now in the past there were actual lists of, you know, very specific recommendations, you know, x numbers of studies in x, y, or z.

DR. DANIELS: And so that's the next thing. Once we're kind of done talking about this outline, I don't know if there are more comments about the outline or, for example, other ideas for barriers to research or policy or other thoughts about what our needs are. But, once we're done with that we'll move onto talking about objectives.

DR. KOROSHETZ: Let me just run down people's thoughts. So the, if you just look at the what do we need section. So, one was the brain development issue looking at utero, first two years of life, I

think Shafali was, I think that was to your point Shafali.

DR. JESTE: Yes.

DR. KOROSHETZ: And then I remember that Kevin Pelphrey made a strong comment about always trying to look for potential adaptive brain changes in response to a developmental disturbance. So, I put that in there as well and maybe in another place as well. Are people comfortable with that idea?

DR. REICHARDT: Yes.

DR. BATTEY: Yes.

DR. DAVIS: Yes.

DR. JESTE: Sounds great.

DR. KEVIN PELPHREY: Yes.

DR. KOROSHETZ: And then the next one too was really trying to get at the tissue issue that (Lou) brought up. So, getting better knowledge of what's going on really requires brain tissue. I thought there'd be a couple of things to stress that certainly the cell type work is exploding in brain and we'd like to, you know, once there's knowledge about all the different cell types and their abundance and ratios and typical development.

We'd like to look at that in autism I suspect. And similarly with the ability to look at connections between different cells in the nervous system, that's moving quite rapidly.

DR. BATTEY: That's absolutely a growth area for the next five years.

DR. KOROSHETZ: Okay. And…

DR. REICHARDT: It's extraordinarily powerful insight to expression and patronymic methods that

are being developed. Some of which are probably conservative signatures of activity in the living brain. I'm certain.

DR. KOROSHETZ: Insight, okay good. And then, so chromatin remodeling is brought up a couple of times. So, is that something that would then have to be studied in human tissue? Is that correct or?

DR. REICHARDT: I think it realistically does, yes.

DR. BATTEY: Really? I'm not so sure.

DR. REICHARDT: Well, I think it's because, so the enhancers and some are not well conserved in terms of position in that, in model organisms. And so if you're going to look at impacts and CMV's or particularly changes on chromatin remodeling to really look at specific impacts. You almost have to look at the right organism.

DR. BATTEY: I don't see how an animal model is going to be terribly helpful. I mean…

DR. REICHARDT: No, that's right. Yes.

DR. BATTEY: Just look at what happens to the old factory bulb in different animals. Compare the size in humans, the relative size to the relative size in mice for example.

DR. DAVIS: Yes. On the flipside of that though, that, you know, the old factory system is something that is highly developed in specific organisms in specific ways. And ones that argue the same thing about the forebrain, but if you step back and ask about, you know, the basic molecular biology itself. I think that, not to the exclusion of meeting society needs, but I wouldn't necessarily restrict it there.

DR. BATTEY: I don't disagree with that.

DR. KOROSHETZ: Okay. And the next one was the circuit abnormalities. I think we talked a little bit about that already. And the idea that Louis is mentioning, add in the impact of genes and immune system activation to specific cells and circuits need to get to the synapse level. And then the next one was the molecular part. And we got some feedback there. Any things to add there?

Also, I put in about, in both the circuit and the neuro effects of genes implicated the thought looking at the effect of xx versus xy and sex hormones to get at the gender differences. Okay, and then the last one was more of the phenotyping issue that was brought… No, go ahead.

DR. DAVIS: The last thing that occurred to me is neuromodulation actually. And I just wanted to throw that out there and maybe Louis could comment. Perhaps he thought more about this than I have. Whether that would be something that hasn't reared its head yet but might be along the lines of the immune system as well.

DR. REICHARDT: I think it's very good. I mean, particularly I had a bit of neuro counts and oxytocin. I mean, some of the, virtually time for therapy, you know.

DR. DAVIS: I mean on the circuit side.

DR. REICHARDT: Yes.

DR. DAVIS: Circuit or molecular, however that points. But I think it should be represented in there somewhere.

DR. KOROSHETZ: Got you, okay. Okay, and then I guess we get barriers. There was a lot of discussion about the need for large studies and so (unintelligible) did say there is still a need for innovative single definitive to continue. But a growing need to kind of do things more systematically. I think that came up multiple times.

DR. REICHARDT: I think they're going to have to express the need for very large cohorts. I mean we're talking about this is important for the genetics, it's important for the phenotyping, it's, you know.

DR. KOROSHETZ: And then there was a…

DR. JESTE: I would say large, I would just say here, I mean I think this is for large cohorts, but also infrastructure to ensure that methods are collected in a consistent way, right? Which is less, you know, we have these great systems in place, we're making sure there's reliability on the ADOFs and these standardized measures.

But, very few of these same, you know, the same kind of infrastructure for E, G, or I tracking. And I think that's a really, that needs to be a key priority if we're going to have relevant sample sizes for these imaging modalities.

DR. KOROSHETZ: Okay.

DR. REICHARDT: And one needs better, one needs development or methodologies that are appropriate for assessing various behavioral abnormalities in very large cohorts. You know, web based IQ, web based motor function (unintelligible) for example.

DR. JESTE: Right.

DR. DAVIS: And I think in addition to what Shafali said and your valid point. I think also tying in with the large samples, the idea of reproducibility. Because I think we have many studies of potentially informative tools in small samples. But they haven't been replicated in these large samples. So, we don't know that they work consistently. We don't know individual differences.

DR. KOROSHETZ: So I had that down in one of the policy issues was to address replicability of

findings by follow up allegation studies. And then actually developing guidelines for ASD research, and (unintelligible) for prospectively planned data sharing. And the (unintelligible) of behavioral measures. Does that fit where your, is this…

DR. MCPARTLAND: I think if it's there as well, I think that it's useful to tie it into the large samples. I think one of the problems is that we don't note to what degree the heterogeneity we've seen is because of small samples and applying some of these things in large samples would help understand individual differences better.

DR. KOROSHETZ: And who's talking? I didn't recognize your voice.

DR. MCPARTLAND: Jamie McPartland.

DR. KOROSHETZ: Jamie. Okay, great. Okay, super. So, the other needs were longitudinal studies as opposed to cross-sectional studies. That make sense to folks?

DR. JESTE: Yes.

DR. DANIELS: Definitely, yes.

DR. KOROSHETZ: And then the animal models. Anything to add there? I put in a mention of nonhuman primates as a potential model going forward.

DR. REICHARDT: We should probably add rats to that.

DR. DAVIS: Yes, I would agree.

DR. REICHARDT: And also fish actually. I mean I have their different uses, but I think if ones, I think it's, it would be very useful just to mention the variety of models. It's not really just primates, it may be helpful.

DR. KOROSHETZ: Yes, okay. And then what about the, so the other area, which has always been bugging me is, seems like we know very little about whatever the environment is doing. If I had to think of a barrier, that seems to be the biggest one. Does anybody have a sense of how, where that feel might be going?

DR. REICHARDT: I think it's limited by cohorts. All the studies that are, I think the vast majority of studies have been Scandinavian cohorts, where they just are not large numbers of people and Norwegian. I mean, we're not just talking about external environment. We're talking about environment in the womb first.

DR. KOROSHETZ: Right. So, I put that in there, in utero. Which Shafali, how would anybody ever get to that? How would…

DR. JESTE: I know, it's a great question, it's actually funny, I gave a talk at a cognitive neuroscience conference earlier this year on the infancy work. And, you know, TSC and familial risk. And one of the big topics that came up in discussion was why, you know, how can we look better at the in utero environment. Because maybe that would shed light on some of the variability and outcomes.

And so, you know, people talked about looking at maternal factors, right. So, you know, maternal stress hormones and other things. And just getting a better sense of parental genetic environment. Which, you know, seem like actually kind of low hanging fruit that we haven't pursued so much.

I mean, it's tricky because it's hard to sort of ask a parent when you're studying infants at risk, right, because there is, you know, you have to be careful about the implications of that. But I think that, you know, I think that there's a huge, wide-open door there for us to think really carefully about how we would study, you know, the prenatal environment.

But I agree, I think that's a very important kind of quote-unquote environmental piece that we haven't really dug into enough.

DR. DANIELS: So, this is Susan just to remind you all, there is a question three that's all about environmental and genetic risk factors for autism. So, that group is going to be getting into this. But it doesn't hurt for you to mention some areas of interest. But I think that that group will be digging into it much more deeply.

DR. KOROSHETZ: Yes. No, I think, I was at, the point was, you know, if it's hard to get a causation if you're missing, you know, a big chunk of the causes.

DR. DANIELS: Right.

DR. KOROSHETZ: You know, that's, so I mean we're working off the gene, genetics findings, but they're hard and we can explore them in terms of their effects on development and circuit function. But at the other piece, you know, if we knew that there was something there. Are there any hard data in terms of stresses leading onto autism?

DR. JESTE: Well, sure. At the Mayan Institute, there's both the charge study lead by (Irva Hertz Pachodo) and the marble steps.

DR. DANIELS: Right.

DR. JESTE: And she's been looking at environmental influences and a large cohort of young kids at the time of diagnosis. And sound things like air pollution or the importance of prenatal supplementation, things like that. So, there are studies out there.

It could be added to our large, you know, our dream large cohort of kids starting at infancy to add onto there a really comprehensive look at both maternal and outside environmental factors. So along with this cohort. So really deep phenotyping

beyond just the child, but they're environment as well.

DR. CHAWARSKA: There's quite extensive research on the effects of maternal stress, anxiety, and depression during pregnancy. And altering development of brain and functional connectivity. We don't have as much of these kinds of studies in autism. But, I think that's area that's very important that's heavily, heavily understudied in our field.

DR. KOROSHETZ: And some of those things…

DR. JESTE: Yes. There is quite a literature on this in, you know, in non-neural developmental disorders, just in, you know, large typical development studies if you will. And people looked at also more recently things like maternal health, you know, BMI and maternal obesity being a risk factor for, you know, certain developmental outcomes and that sort of thing.

I think it just hasn't translated yet to autism because we're still trying to figure out, you know, can we identify early, you know, brain markers in these babies after they're born. So, but I think there's and opportunity to kind of combine the two levels of investigation, you know, and kind of larger perspective studies if we were able to do that.

DR. CHAWARSKA: And at this point, desirables usually enter this sort of co-various into the models. And I think this is time to treat them as really part of variables.

DR. KOROSHETZ: Okay. In terms of the other barriers, any, so we're down to number five, little knowledge of how to design therapeutic interventions to improve brain function in ASD. I guess that's kind of an obvious one, as we don't have really good interventions. And then few targets for therapy development.

Again, that's kind of obvious as well. Any other barriers that we want to put in? Availability of brain tissue is usually something. Other barriers people want to add to the list?

DR. REICHARDT: I think we need to, I would just say one barrier is the ability to develop methods to target therapeutics quite specifically. Since many of the pathways that have been involved, do very important bodies. The one, might want to address in autism in fact have important functions elsewhere or even within the brain.

You don't necessarily want to effect inhibitory synaptic function, for example, everywhere in the brain. What is good in one place, may be very bad in the other. And so we need development of methods to target brain therapies basically.

DR. KOROSHETZ: Yes. Okay. And then the policy issues, these were the list that I recall from our discussions, inclusions of persons on the spectrum in research plans and messaging. Tracking quality of life across the lifespan. Replicability of findings, moving to larger team studies for the large studies we talked about. And then attracting other folks into the workforce.

DR. REICHARDT: I would say, and I don’t know, maybe you think you got rid of under (unintelligible) I'd say incentivizing individual participation in research efforts. We have to make it worthwhile for people.

DR. KOROSHETZ: Yes. Okay and how about the aspirational goal, the wording of that? So that, let's see, Susan sent out one earlier which…

DR. DANIELS: Right. So, the aspirational goal that I put together based on what Walter had emailed to the group and what we discussed last time on the call. The wording that we have, well let me just read you the current wording just to remind you of what it said before. It said

discover how ASD effects development, which will lead to targeted and personalized intervention.

And the new version would say discover how alterations in brain development and brain function lead to ASD in order to enable the development of the effective targeted interventions. And societal accommodations that improve the quality of life for persons with ASD.

DR. KOROSHETZ: A mouthful, but it's excellent.

DR. REICHARDT: That's good.

DR. JESTE: I like it.

DR. DAVIS: Yes, that's good.

DR. KOROSHETZ: Okay good.

DR. REICHARDT: The only limitation of that is there is evidence for example sensory, hypersensitivity as these may not just reflect all durations inside the brain.

DR. KOROSHETZ: Good point. Peripheral nervous systems always gets put down, I don't know why. Okay. All right, so…

DR. JESTE: How many neurologists care about the peripheral nervous system, Walter?

DR. KOROSHETZ: Hey man, it's important. The (unintelligible) nervous system is even more important, and that's even worse, more forgotten.

DR. JESTE: No, I agree. I said estronologist, but there's not so many of us too.

DR. KOROSHETZ: Okay. So, let's see. So…

DR. DANIELS: To get that, you could, this is Susan, where you say alterations in brain development, you could after that say and nervous

system function, which would include brain as well as peripheral nervous system.

DR. KOROSHETZ: Yes, that's true. Yes. Now that's getting clever, very good. Okay. So, that's kind of…

((Crosstalk))

DR. KOROSHETZ: So, people have to work the outline as it stands then? With diet we can make all these changes and maybe move the emphasis around based on the discussion today as well. Does anybody else have further comments on the outline?

DR. REICHARDT: Not at this time, sorry.

DR. DANIELS: All right. Well, I think then we are ready to move on to discussing objectives. Which I think for question two is probably one of the hardest ones just because you have so many different diverse topics that you cover in this chapter. But trying to consolidate into three broad objectives. And you could, under these objectives, put examples from several different fields.

So, but the committee had decided that we were going to go for three objectives per chapter. The team here in OR tried to put together three suggested ones that were based on your discussion. But you can of course propose anything else that you would like.

One of the themes that we heard you discussing was the idea of taking phenotypic and genetic data to examine the biological basis of ASD including systems biology and developmental context. That's something that came up in previous.

That also talked about the underlying biology of co-occurring conditions, looking for treatment. Which I think has been a theme that's carried through from previous versions of the strategic plan. And talking about integrating research

across many different areas of science and forming big collaborative teams.

So, those were three possible themes, but it's really open to all of you to come up with three themes that you think would capture the major direction that you'd like to see the field move in, in the next few years. So, please go ahead and make your suggestions.

DR. KOROSHETZ: What was the first one? Could you just go through?

DR. DANIELS: Sure, I'll just reread it. It's on the agenda. It says, undertake studies utilizing phenotypic and genetic data to examine the biological basis of ASD including in systems biology and developmental context. So, I don't know if that even captures what you interested in. Wordsmithing is another whole level. But first try to figure out what themes you want to capture.

DR. DAVIS: Perhaps, you know, one way to think about this would, probably this is already what you're thinking about this. So from, you know, sort of cells, circuits and organisms, that treat as narrative.

DR. DANIELS: So, then you would be talking about having the three major areas of emphasis, the three objectives, one being about cells, one being about circuits, and one being about organisms?

DR. DAVIS: I don't know, it just seems that there are three levels of scale that one is really sort of going after. Each one obviously is going to be interwoven with the others. You don't want to do (unintelligible) being done in isolation for sure. But each could be focused at a different scale.

DR. KOROSHETZ: Anybody have thoughts? I mean that's kind of how we approached the science.

DR. DANIELS: So, do you have a proposal of, for example if you were to have an objective that was about the cellular level, what it would, how you would word it?

DR. KOROSHETZ: Yes, we could work on that. I think that's kind of getting at the pathways abnormalities.

DR. DANIELS: Something that would be a little bit challenging about using that approach is that we use these objectives to code categories for the strategic plan. And I think a lot of your research projects may involve more than of those. And so it would be pretty difficult to categorize them according to that.

Because something that involves cellular biology may also involve circuitry. And so then it would create a kind of an issue for trying to separate those.

DR. FENG: Yes, we'll probably have to think about different (unintelligible). What are the three major things if we saw we were pushing the field forward. Whether it's these mechanisms are (unintelligible) are treated (unintelligible).

DR. REICHARDT: I could only wordsmith, but I would argue that you should probably include genetic and non-genetic risk data, not just genetic data under number one.

DR. DANIELS: I see.

DR. FENG: How long is this objective? For five years? Or for 10 years?

DR. DANIELS: Five. So, and especially…

DR. DAVIS: For example, I totally understand the desire not to categorize things according to scale, that makes sense. So, what if the first one began as a sort of, you know, driving from the cellular basics to human phenotype?

And then, you know, the second one could be cutting across from a different starting point, but ultimately each one ends up with an effort to arrive at a common understanding. So, what you're looking at are essentially trajectories rather than categories.

DR. KOROSHETZ: So, what would be the three trajectories you're thinking of? Is it three different trajectories? Is that what you're getting at?

DR. DAVIS: Yes, I can only really comment on the first one. My expertise isn't in the other. So, one could imagine something like, you know, pursuing the sort of genetic polygenic and environmental kind of basis beginning at the cellular level and expanding to the structural and functional modifications that occur at the basis for autism.

And again, we've missed this critical piece once again and there of it, that needs to be in the wordsmithing of connecting between the, you know, ultimately the imaging studies and the underlying genetics. There is that world in between that was highlighted earlier that needs to be in there somewhere. But that could be a trajectory.

DR. KOROSHETZ: So, that would be objective number one. I think we could work with that, yes.

DR. DANIELS: So, with these broad objectives, you don't necessarily have to throw in like every specific word like imaging and so forth. You can put examples underneath the objectives if you can word them very broadly. But then, if you want to provide examples of the kinds of studies that might be appropriate, I would recommend no more than five.

Because I think it would get hard to read if you have a lot of examples. But if you wanted to provide those examples, you could throw in some

examples to be more specific. But, to keep the wording very broad.

DR. KOROSHETZ: Okay. I guess one question I have, Sue, is taking up an entire recommendation with the large scale team research. To code for that, I imagine that's a small portion of what you would be seeing now.

DR. DANIELS: Right. Well, what we anticipate in terms of what we will be coding under the new strategic plan is that since we're having many fewer objectives, the last strategic plan had 78 objectives, and this new one will have about 20 or 21. That there will be a lot more that will fall outside the objective, but then we have that subcategory coding, captures everything. And so I think we'll be relying on that to tell us what else is in the portfolio.

DR. KOROSHETZ: And from the other calls, do you think that's a common…

DR. DANIELS: I think it is. I think that you, the question two group may have probably about the hardest task. Because I think the others came up with their themes a little bit more easily. And they've fallen right out of the calls. And so, we haven't had that much trouble coming up with three good themes.

I think that because there's so many different fields of biology covered here, that it makes it a little hard to start grouping them together under an umbrella to make themes out of them. But this first one that you're talking about with genetic and polygenic causation et cetera.

I guess, as long as you stay away from like really causation because that's question three. But, those components of the biology, I think that that could be worked into something. But you would have to come up with another couple of themes that are distinct.

DR. KOROSHETZ: I was asking about the last theme you mentioned. Was integrated research and more team research.

DR. DANIELS: Right, right.

DR. KOROSHETZ: Is that common to most of the other groups as well? Or not?

DR. DANIELS: Not that particular theme, no. They have, most of them have kind of themes based around the science itself or the implementation or like kind of broader societal goals. Kind of things depending on if it's a chapter that's more related to services.

DR. KOROSHETZ: Can we emphasize if data can be a theme, emphasize in longitudinal environmental studies from, or aspect from (unintelligible) to animal model studies?

DR. DANIELS: Yes. And that's something that some of the other groups are very interested in as well. But I don't think it's shown up as an objective as yet. So, I think question three is also interested in that, but if you ended up having it in question two, that would be fine if you wanted to say that that's one of your top priorities, is creating these large longitudinal studies.

DR. FENG: I think from both animal studies and the (unintelligible) critical (unintelligible) in the standard ASD.

DR. KOROSHETZ: Why do you say in the animal studies? What's peaking your interest there?

DR. FENG: Animal studies because for animal studies you can actually dissect the molecular studies. A (unintelligible) at a different study, stage, you cannot get a tissue (unintelligible) from doing a single lab or other molecular studies. Just there's no ways of getting enough tissues from (unintelligible) and how you can

change the, relate to circuit change. That can also circuit (unintelligible). The animal model is the key to understand this.

DR. KOROSHETZ: Got you.

((Crosstalk))

DR. FENG: We would be validated in the human, but of course in this kind of study, you cannot just get whatever age you want for human patient brain tissues.

DR. KOROSHETZ: Right. So, what do people think about the choices? So, the first one would be getting at the biologic basis of both this systems biology, the circuits and cellular dysfunction. And then the third one would be this idea of large longitudinal studies of animals and humans. And then the middle one is understanding the co-occurring conditions better.

DR. FENG: That's probably very good. Co-occurring conditions especially individual, you know, sole variable, so many of them. Probably very important. Some of them so debilitating.

DR. KOROSHETZ: Yes. What do people think about those three things then?

DR. REICHARDT: I can live with that.

DR. KOROSHETZ: Okay.

DR. BATTEY: Walter, those three sound pretty good to me.

DR. KOROSHETZ: Okay, so maybe we'll try wordsmithing those out and sending them around.

DR. DANIELS: That sounds like a good idea.

DR. KOROSHETZ: Thanks.

DR. DANIELS: So, I think with that, for that first one would you include things about heterogeneity and subtyping? That was something that seemed like it was a major theme on the call today. Would that fit in there?

DR. KOROSHETZ: I think that'd go in the third one.

DR. DAVIS: Yes.

DR. DANIELS: On the third one, right.

DR. KOROSHETZ: The large studies, yes.

DR. DANIELS: Yes, because that seemed like something you were really interested in. So, that sounds good. So, you've actually then, if you are happy with these three areas for themes and having some members of the group work offline on them and bring them back to you.

We've already discussed the aspirational goals. On the title, how can I understand what is happening, was there anything that you wanted to change about that? I guess on the last call you didn't seem to think that needed a change, but I want to let you have another chance to reflect.

DR. KOROSHETZ: I think…

DR. DANIELS: You'll be good with how can I understand what is happening?

DR. KOROSHETZ: I think so.

DR. DANIELS: Great. So, you've made a lot of progress in terms of talking about your outline. I think your group does have the most developed outline at this point, so that's a good thing. So, after this call I'll be trying to circle back with Louis and Walter about the outline and they will be getting in touch with various members of the working group to see who might be able to help out with drafting certain parts.

We want to keep in mind we're writing for lay audience, so try to write for the family of an affected child or an affected adult for an adult on the spectrum, in language that they can understand. And describing the major highlights of what's going on in the field and where it's going.

So, you should be hearing from either Walter or Louis about being tapped to write certain areas, if there are areas that you're interested in writing on, please let the three of us know so that we can be sure to include you in some of that. And then the whole chapter…

DR. REICHARDT: Better make your picks now or you'll be left with the drags at the end.

DR. DANIELS: Yes, on the call right here, if there's anybody who wants to volunteer for anything.

DR. REICHARDT: Or you can send, they can send an email. We have the structure so you can say which piece you're interested in, yes.

DR. DANIELS: That would work. And so, once the draft is together it will circulate to the entire group. And so you can all comment on various sections. And we'll be bringing the objectives and whatever draft that you have available back to the committee which is meeting on January 13th, to review and discuss what's been prepared by the working group.

I know that the committee greatly appreciates the efforts of all our volunteer members of this working group helping us put this together. So are there any questions that anyone has about…

DR. KOROSHETZ: January 13th is a, what is, that's a kind of a draft copy? Is that what it is?

DR. DANIELS: Yes, so we'll…

DR. KOROSHETZ: That we get feedback on.

DR. DANIELS: Yes, exactly. So, we'll try to get drafts from all the working groups, bring them to the committee. The committee especially will be looking at the objectives and seeing if they approve those objectives and they can look through the text that you have.

I think that given just where we are right now and almost at December is probably going to take a little bit more to get everything polished up. But we hope to publish, you know, in the spring or so, sometime during. So, are there any other questions about the process here? Or anything we've discussed?

DR. BATTEY: So, Susan, you've been very helpful. Thank you.

DR. DANIELS: Thank you.

DR. KOROSHETZ: Sorry, (Susan), I got one question. We're probably the best group, right?

DR. DANIELS: You're an excellent group. Great group.

DR. KOROSHETZ: All right, great.

DR. DANIELS: All the groups are great. We've really appreciated everyone's effort and I think you've all been very thoughtful and thank you for all your help. So we will be in touch after the call by email. And let us know if you need anything. Thanks again for joining this call.

DR. KOROSHETZ: Thank you.

THE GROUP: Bye.

(Whereupon, the conference call was adjourned.)