U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

STRATEGIC PLAN UPDATE

WORKING GROUP 3 – QUESTION 3 – WHAT CAUSED

THIS TO HAPPEN AND CAN IT BE PREVENTED?

CONFERENCE CALL 3

WEDNESDAY, DECEMBER 7, 2016

11:30A.M.

PARTICIPANTS:

SUSAN DANIELS, PH.D., EXECUTIVE SECRETARY, IACC, DIRECTOR, OFFICE OF AUTISM RESEARCH COORDINATION (OARC), NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

DAVID AMARAL, PH.D., DISTINGUISHED PROFESSOR DEPARTMENT OF PSYCHIATRY & BEHAVIORAL SCIENCES RESEARCH DIRECTOR, THE M.I.N.D. INSTITUTE UNIVERSITY OF CALIFORNIA, DAVIS AND CO-CHAIR, WORKING GROUP 3

CINDY LAWLER, PH.D., CHIEF, GENES, ENVIRONMENT AND HEALTH BRANCH, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES AND CO-CHAIR, WORKING GROUP 3

RAPHAEL BERNIER, PH.D., ASSOCIATE PROFESSOR, DEPARTMENT OF PSYCHIATRY & BEHAVIORAL SCIENCES, CLINICAL DIRECTOR, SEATTLE CHILDREN'S AUTISM CENTER

DANI FALLIN, PH.D., PROFESSOR, JOHN HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

ALYCIA HALLADAY, PH.D., CHIEF SCIENCE OFFICER, AUTISM SCIENCE FOUNDATION

IRVA HERTZ-PICCIOTTO, PH.D., DIRECTOR, UC DAVIS ENVIRONMENTAL HEALTH SCIENCES CORE CENTER, PROFESSOR & VICE CHAIR FOR RESEARCH, DEPARTMENT OF PUBLIC HEALTH SCIENCES, DIRECTOR, MIND INSTITUTE PROGRAM IN ENVIRONMENTAL EPIDEMIOLOGY OF AUTISM AND NEURODEVELOPMENT

ELAINE HSIAO, PH.D., PROFESSOR, LIFE SCIENCE, INTEGRATIVE BIOLOGY, AND PHYSIOLOGY, UNIVERSITY OF CALIFORNIA, LOS ANGELES

CRAIG NEWSCHAFFER, PH.D., PROFESSOR, DIRECTOR, THE AJ DREXEL AUTISM INSTITUTE

STEPHAN SANDERS DR. STEPHAN SANDERS, PH.D., ASSISTANT PROFESSOR, PSYCHIATRY, UCSF SCHOOL OF MEDICINE

LAURA SCHIEVE, LAURA A. SCHIEVE, PH.D., TEAM LEAD, EPIDEMIOLOGY TEAM, DEVELOPMENTAL DISABILITIES BRANCH, DIVISION OF CONGENITAL AND DEVELOPMENTAL DISORDERS, NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES CENTERS FOR DISEASE CONTROL AND PREVENTION

PROCEEDINGS:

DR. SUSAN DANIELS: Thank you. Welcome to our listening audience and to the working group, including our two co-chairs David Amaral and Cindy Lawler. We are going to be holding our third conference call of the (IACC) Strategic Plan update working group for question 3, what caused this to happen and can it be prevented, that's about environmental and genetic risk factors. This is going to be our last phone call before we start working on the writing portion of updating the strategic plan and on today's call we're going to be talking about the outline for your chapter and then the objective that you'd like to create for your chapter.

So before we begin, I'd like to do a role call just to see who all is on the phone. I'll start with David Amaral.

DR. DAVID AMARAL: Here.

DR. DANIELS: Thank you. Cindy Lawler?

DR. CINDY LAWLER: I'm here.

DR. DANIELS: Ruth Etzel? Allison Singer? Rafael Bernier?

DR. RAFAEL BERNIER: Yes, I'm here.

DR. DANIELS: Thanks. Evan Icheler? Danny Fallin?

DR. DANI FALLIN: I'm here.

DR. DANIELS: Dan Geschwind? Alycia Halladay?

DR. ALYCIA HALLADAY: I'm here.

DR. DANIELS: Irva Hertz-Picciotto?

DR. IRVA HERTZ-PICCIOTTO: I'm here.

DR. DANIELS: Elaine Hsiao?

DR. ELAINE HSIAO: Here.

DR. DANIELS: Craig Newschaffer?

DR. CRAIG NEWSCHAFFER: Here.

DR. DANIELS: Elise Robinson? Stephan Sanders?

DR. STEPHAN SANDERS: Yes, here.

DR. DANIELS: Joan Scott? And Laura Schieve?

DR. LAURA SCHIEVE: I'm here.

DR. DANIELS: And Laura is joining us from CDC. So she wasn't on the first two calls, but has now joined our group from the CDC perspective. So to begin our discussion today, I'd like to turn your attention to the chapter outline, which isn't exactly an outline. It's more of a list, but we tried to put together topic that came up on the last two phone calls that you all discussed and tried to organize them a little bit according to some of the categories that you discussed on your call.

I wanted to go over this just to make sure that we list all the topics that you're going to want to touch on in your draft chapter. So some sub-topics that were included under understanding genetic risk factors, which I know we have a few more geneticists on the phone today than we've had in previous calls. The topics that were discussed on previous calls were -- identification of risk genes in human populations, genome wide and sequencing studies, genomics and proteomics, heritability of autism, genetic testing, risk communication around genetic testing, data access and data sharing across scientists and workforce needs in the genetics area.

Are there any other topics that you think would be really important to include in the chapter updating us on the most important science advances that have been made, as well as what the major needs are for the field to move forward?

DR. SANDERS: Stephan here – a couple of comments. It should probably be risk variance instead of risk genes, to break the non-coding region. And with genomics and proteomics we should probably include the transcriptome and epigenome in that since they work in concert. In terms of missing topics, I'd say genomic architecture. And by that I mean particularly how do these – all of these different genetic and environmental risk factors combine to actually – as a result of the phenotype? You could potentially combine genomic architecture and ASD inheritability.

DR. DANIELS: Okay.

DR. AMARAL: And, (Susan), this is (David) – I think, you know, sex differences is one topic that overlaps maybe with workgroup 2, but I think it should be included here as well.

DR. DANIELS: Sure. I think that that's fine. It doesn't hurt to talk about the same topic maybe from a slightly different perspective in the different chapters. We can add that. Anything else that you see missing in this section?

(No response.)

DR. DANIELS: Okay, if you think of something as we're going along, let me know.

DR. SANDERS: I'm sorry, so one of the functional studies. So you're following up the genes in (unintelligible) IPSC models.

DR. DANIELS: So you can mention that. I think question 2 deals with that more, but we can mention it here too.

DR. LAWLER: This is (Cindy) – I think that kind of more functional genomic fits well under the third part of this chapter as well.

DR. DANIELS: Okay.

DR. LAWLER: They link it – because that's about kind of how these risks – risk variance, (unintelligible) – to kind of, you know, pathways.

DR. DANIELS: All right, so I'll put that down there as well.

DR. LAWLER: (Unintelligible) that allow you to kind of look at more, you know, mechanistically. And that would include, you know, the stem cell studies, some of the animal model studies.

DR. DANIELS: Okay.

DR. LAWLER: This is a question for the geneticists on the call, but you know, I'm wondering if in that first section there should be something about this issue of, you know, shared risk or, you know, the specificity of the risk factors for autism versus some of the other kind of conditions.

DR. AMARAL: Yes.

DR. LAWLER: And that understanding of, you know, that – those kind of boundaries or, you know, that just are officially talking only about the risk for autism maybe that doesn't reflect the advances in the field.

DR. SANDERS: I think that's a very good suggestion. It slightly overlaps with the genomic (unintelligible) genomic architecture question. But I think that (unintelligible) out of the – I guess extending to related phenotypes. I think it's very important.

DR. DANIELS: Great, anything else?

DR. NEWSCHAFFER: (Susan), this is (Craig). I'm sorry – just by way of process. So we're adding to the list now and the way the call is going to work – are we going to come back and discuss these or is this our only opportunity to comment on anything related to that section?

DR. DANIELS: I mean throughout the call you can always feel free to throw in something, even if we've moved on to another topic. You know, the whole call is open to whatever you need to say, but this is a moment that we're talking about this. So if you think of something that has to do with genetic risk factors that you want to discuss, feel free. And what we're going to do in (O-Arc) is we'll try to update this list and then we'll give it back to the chairs to see what they want to do with it before they start helping to put together the people who will be writing various aspects of this.

DR. NEWSCHAFFER: Okay.

DR. DANIELS: So we'll update it and make sure some of these items that you're mentioning now are included. Anything else related to genetic risk factors in particular?

(No response.)

DR. DANIELS: All right, so moving to the second portion on understanding environmental risk factors, individually and in combinations over time. Some of the topics that the group has discussed have been environmental exposures, including chemical, nutritional, social stressors and other types of environmental exposures, both pre-natal and post-natal influences, epidemiological studies of risk factors, the need for improved tools for exposomics, data access and data sharing, which is a common theme probably across most of the strategic plan and workforce needs in this area. Are there some other topics that you'd want to make sure are included?

DR. LAWLER: So this is (Cindy) – I don't think the need for improved tools for exosmic – that might be a little too specific. Because really, yes, we need that and it's more that kind of application of those tools to questions about autism, but really just any advances in the exposure science that will, you know, allow the epidemiological studies to, you know, assess exposure more reliably would be helpful. And that, you know, could be individual, you know, chemical, other exposures of, you know, smaller combinations of, you know – pesticides, for instance. Not necessarily just new methods that are going to capture the universe of exposure. So maybe some rewording of that.

DR. DANIELS: Yes, so (unintelligible).

DR. LAWLER: (Unintelligible).

DR. DANIELS: Yes, so you said maybe like the need for advances in exposure science and you said that will allow epidemiological science to more accurately assess exposures? Or what…

DR. LAWLER: Well, I mean, I think it's the application of new methods.

DR. DANIELS: Okay.

DR. LAWLER: Not really the, you know, the development of those isn't necessarily, you know, central to what the (IOTC) is (unintelligible) needs to do. That's a broader goal of exposure science, but it's the – you know, keeping abreast and applying new tools, new approaches as they develop to autism studies is what's needed.

DR. DANIELS: Okay.

DR. NEWSCHAFFER: So - and, (Cindy), this is (Craig). So that could include exposure-wide association studies, but might also include individual applications of improved exposure

assessment in sort of a more traditional hypothesis driven?

DR. LAWLER: Well that's my suggestion.

DR. NEWSCHAFFER: Yes. I think as long as it still allows for consideration of both of those things. I think that's fine.

DR. LAWLER: Yes, right.

DR. SANDERS: I like the idea of trying to highlight the need for the (unintelligible) approach in exposure. I think, certainly, on the genetic side after a long time of candidate gene studies, it's the (unintelligible) approach, which is really had a successful ability to identify true causal risk factors. I think trying to highlight that that same way of thinking is the most likely to yield true casual factors in the exposure side would be useful to do. I certainly appreciate there is a broadening the question to documenting exposure, but it would be nice to see some push toward the (unintelligible) way of thinking.

DR. LAWLER: So maybe that's something we could handle in the writing to really get - have, you know, talk broadly, but then really, you know, have a couple sentences that highlight the – that that is a particular priority (unintelligible) approaches and that has potential to really be a game changer.

DR. SANDERS: Yes.

DR. DANIELS: Yes…

DR. LAWLER: I just (unintelligible) about some – because there is real advances. Even in studying individual chemicals. They can be really helpful in resolving inconsistencies or just, you know, more reliably understanding, you know, prior exposures.

DR. SCHIEVE: Hi, this is (Laura).

DR. HERTZ-PICCIOTTO: Hi this is – oh, go ahead.

DR. SCHIEVE: Oh okay – I guess I just wanted to really ask a question and give a comment. Under epidemiological studies of risk factors, does that include what the major challenges are in some of these studies? I'm thinking of two things – one, sample size is a big issue in terms of being able to assess sub-groups and I'm not just thinking of genetic sub-groups, but things like girls versus boys or (ASD) sub-groups. And the other thing is challenges in differentiating risk factors that might clump together. The example I'm thinking of is differentiating anti-depressant effects from depression of anxiety effects. That may already be what you guys have been thinking about to discuss under epidemiologic studies generally.

DR. HERTZ-PICCIOTTO: Those are definitely challenges that are part of, you know, what every epidemiologist thinks about as they're doing studies – and particularly for medical interventions. That the indication – being able to separate the indication from the intervention and that's a specific example and I think that could be useful to include. It seems to me that, you know, everything that epidemiologists, you know, are concerned about – issues of confounding, how do you really identify what is the driving factor when factors do tend to, you know, cluster – it's just part of how we do the work in making sure we have adequate sample size and not, you know, attempting to do, you know, things that are beyond the scope of given a particular sample size and all of that. And I think, you know, I mean these are what standard textbook epidemiology talk about all the time, but there are specific issues that, of course, arise in regard to autism that need to be highlighted

DR. SCHIEVE: Right. And I was just thinking in terms of some of the specific more emerging risk

factors, like anti-depressants, that there are few risk factors here that those are particular challenges to. Anyway.

DR. HERTZ-PICCIOTTO: Yes. I also wanted to add – I wanted to make a point, besides responding to that, that I think this section also needs to include the biomarkers of exposure that can help with understanding, not just environment in relation to an outcome, but that pathway of mechanisms that are involved and understanding those mechanisms is also a way of understanding what environmental factors are – you know, how they relate to ASD and even where we should be looking when we do understand more about the mechanism that a particular exposure induces and an example would be where we have, you know, we have a lot of genetics pointing to, you know, synaptogenesis related genes as being important.

So we know synaptogenesis probably plays some important role in autism and we also have environmental factors that operate at the synapse. So I think understanding the mechanisms for environmental exposures, including understanding and identifying biomarkers, is part of the environmental piece that needs to be emphasized. And those could be metabolomics, they could be – you know, they're immunologic. Some of the things that are listed under linkages between genes and environment, but some of them may not be related to genes at all. You know, except through – not directly, but you know, indirectly. I would want to have that go under the rubric of understanding environmental risk factors.

DR. AMARAL: Just going to raise the point that Irva just mentioned, that mix that we're missing is metabolomics. And it could either fit under this heading or could easily fit under the genes by environment heading, but I think there are increasing numbers of metabolic studies related to autism – either undergoing – either ongoing or that have been completed. And, you know, they are sensitive to exposure to environmental

contaminates and things like that. So I was surprised, in fact, that it wasn't listed any place on this list and I think we should certainly highlight it.

DR. LAWLER: (David), this is (Cindy) – I think that's a great point. Most of the approaches that are being used to look at the exposomes are, indeed, metabolomics approaches, but it – you know, it's not the same as, you know, there could be many ways you could think about exposmic. I agree that that maybe calling that out could be really helpful, especially, you know, it can be biomarkers (unintelligible) disorder itself, you know in addition to biomarkers of exposure. So it's just – I guess I agree that we should mention it, but not only in the context of expososmic, but (unintelligible) utility.

DR. SANDERS: I wonder if we're in a bit of a mess here by where we're putting things downstream of genes and environment. So in the first section we've got genetics and we expect genetic risk factors to be a causal risk factor and then downstream of that we believe they act through epigenetics (unintelligible) and then ultimately to a phenotype. The same is true for the environment. We believe the – there are environmental risk factor that are extremely causal, then they act downstream – presumably through cellular pathways at some part to lead to phenotype. At the moment we've got – in the first category we've got genomics and proteomics. In the second category you've got exposomics and we're not talking about metabolomics.

I wonder if the neat way of doing this is that we have genomics in the first category, so truly finding the causal risk factors, exposomics and other matters of (unintelligible) in the second category, which again is truly finding the risk factors and then in the third category, there we include transcriptome, proteome and metabolome. It recognizing that those are downstream of environment and genetics. And establishing

causation there can be more complicated. I think you'd probably need to broaden the last title to understanding essentially how genes and environment contribute to phenotype.

DR. FALLIN: This is Dani, I generally like the idea. I think there's still a little bit of muddle-ness in that some of the things I think (Irva) and (Craig) were mentioning were ways to improve exposure measurement where you're still interested in capturing primary etiologic factors, but where you have to rely on a surrogate to do that. So it may not be further understanding mechanism. It may be just a surrogate way of marking the primary exposure risk factor when you can't measure it directly.

DR. SANDERS: That's true, but all of those downstream ones (unintelligible) based genetics and environment. And, therefore, to understand it you need to really have your head in both.

DR. NEWSCHAFFER: Well so I agree (unintelligible) Dani was saying – this is (Craig). I mean from a mechanistic perspective I think that's important and I think that supports the idea of including some of these other (unintelligible) technologies as tools that can be used to understand the mechanistic links between (unintelligible) environment. I think there's broad consensus on that. I think they – I think what Dani is trying to underscore is that they also belong under Cindy's rephrased bullet of improved exposure science. So those tools can be used agnostic of mechanism to develop improved metrics of exposure. All right?

There might be signatures detectable through metabolomics or even in the epigenome that are a byproduct of exposure and they serve as a better measure of exposure than say questionnaire other data. So I think it's important that – and we've heard this from a few people – that I totally agree to your point that they need to be highlighted in that third area, but I think they

also need to belong in the exposure science area independently.

DR. SANDERS: But I couldn't argue the same in genetics, that if I look at proteins then I would get an understanding of how genetics is leading to causality?

DR. FALLIN: But proteins aren't typically used as the sole surrogate of genetics in the way that some of these exposure biomarkers may be.

DR. SANDERS: That's true, but in a post-mortem study they are – we actually haven't done it with a protein yet, but if you've done it with RNA, which is essentially that same concept to downstream (unintelligible).

DR. FALLIN: (Unintelligible) you wouldn't want that relegated only to the mechanistic third category because you're still trying to query about the etiologic information. Right?

DR. SANDERS: Yes, but you're – I think the argument that looking at the metabolome gives you insights to the environment is equally true for the genetics. In looking at the – think about something like cystic fibrosis. We don't look for the gene, you look for the metabolic product – the same is true for PKU.

DR. HERTZ-PICCIOTTO: Yes, I think your point is well taken. I think that it's probably more frequently the case in the environmental field that because it's not easy to do environment – you know, an environment wide, you know, work partly because that changes from minute to minute throughout your entire lifetime as opposed to the genetics, which stays constant. So the need for these other surrogates, I think, is more acute in the field of the environmental research. And, you know, an example would be there are, you know, DNA adducts that are very specific to, you know, can be tracked to specific environmental exposures. And those very same exposures you may not be able

to get those for the right time period at all or very rarely, you know, in some of the really extraordinary studies.

So I think it's, you know, maybe we're just arguing on the head of a pin here, but I do think that it's a more acute need and essential component in the environmental field and maybe quite a bit less so in the genetics.

DR. SANDERS: So how can we get to a middle ground here? Recognizing that these downstream, by which I mean RNA, epigenome, proteome and metabolome are important for both downstream genetics and downstream environment. How can we add them in a way that is equal to both of those while still recognizing the fact that maybe those techniques are used more frequently in the environmental side? Which even I am not entirely sure is true. I mean if you think about the epigenetics that goes from (unintelligible) recently looking at (unintelligible).

DR. NEWSCHAFFER: Yes, I'm so sorry to interrupt – this is Craig. I think that maybe we are on that pin that Irva was talking about, but I think that what you're describing belongs wholly in that section 3 with equal emphasis on genome environment and on these techniques helping us unpack mechanism. I think the only extra point we're making is – I agree that these techniques have not been used more in the environmental side, but we need to see whether or not we can leverage them for exposure science purposes specifically. And that's just sort of this little extra piece that's a little bit different. And I don't think it's in any way deemphasizing the importance of these for understanding mechanism from both the genetic and from the environmental perspective and that can be captured in the third section. It's just a little extra piece that needs to go into that exposure science piece in the middle.

DR. LAWLER: Yes, I agree because, I mean, part of what this plan is laying out is the really, you

know, urgent challenges and that is such a high priority in the – on the exposure side of this risk. So I, you know, agree that it merits mention under (unintelligible) – I mean under that second as well and it's just a little bit different than in the genetic arena. I mean logically it would apply to both, but it's – I think it's – what we're saying is it, you know, rises to a really – a level of urgency for the exposure epidemiology.

DR. SANDERS: Do we know that those methods can be interpreted without the genetics? The question we're really posing here is what is the prime driver of signals which we anticipate the future being observed in the (unintelligible)? Is it driven primarily by genetics? By environment? A combination of both? I think there's a risk here that a study which only looked at one of those might not be important. We're trying to set those goals – I worry about sending a message that you essentially can make sense of this without missing kind of the key component.

DR. HERTZ-PICCIOTTO: Well some of us have been saying that about the genetics world for the last decade and have been surprised to see how little interest the geneticists have had in incorporating environment into their studies. So – and yet, you know, I think it's true that you guys have made huge amounts of success without thinking about environment, undoubtedly. And, you know, I think it's probably true on the other side.

DR. SANDERS: So I think that's true…

DR. HERTZ-PICCIOTTO: There's lots that can be done outside of it, but I think it will be far far richer when we get together and start incorporating both into virtually every study that's trying to do etiologic research.

DR. SANDERS: Yes. Well, of course, this is really because DNA is an outlier and has this bizarre consistency throughout your entire life and pre-dates the cause. I think everything

downstream (unintelligible) agree. I mean do we have an opportunity here to send a clear message that we think that's the way this needs to be done by including that comment in the third category?

DR. NEWSCHAFFER: And I don't think anyone is arguing that we shouldn't. I think that – I mean I can't speak for all of the epidemiologists, but I think we're saying resoundingly, yes. We're just saying that because we don't have that happy circumstance with DNA on the environment side that as a tool we could potentially leverage – it's an empirical question. Can we use (OMX) technologies to come up with better measures of exposure and exist otherwise being agnostic as to whether or not those (OMX) signals lie on a mechanistic pathway that leads to autism or it may lie off that pathway but still help us characterize exposure. So, you know, I don't think anybody is trying to de-emphasize the grander way that the data should be used and that's most important. We would just like to get that little extra bit in under exposure science. That's all I think we're asking for.

DR. SANDERS: Shouldn't it go into both though?

DR. FALLIN: I think going to both is great solution.

DR. SANDERS: Yes.

DR. FALLIN: I think going to both is the best solution. I was only pushing back because I would hate to see it removed from the etiologic sections, but I think both is a great solution.

DR. SANDERS: Great, fantastic. And let's include the whole downstream gambit of epigenome, RNA, protein and metabolome.

DR. HALLADAY: And I don't know – this is (Alicia) – I think the way that it's organized probably makes the most sense logistically having genes and then environment and then gene

environment. And I can't say that I'm suggesting a different way, because I don't have one, but it seems like just in the order that the third is kind of the last on the list and really I think what we're discussing here is the integration of genetic and environmental factors to understand etiology you know, kind of as like, you know, the end result. And so I wonder if that's something we should stress.

DR. AMARAL: This is (David) – is there a bullet point that you'd like to propose adding or – so can you sort of boil down your issue to a suggestion for how the outline might be altered?

DR. SANDERS: Sure, absolutely. I might actually help with the language, but – so let's take the second bullet point (unintelligible) genome wide and sequence those genomics. Let's remove proteomics from that. We could maybe call it genomic studies and then after that genome wide and sequencing studies. Actually, even that doesn't make sense. It needs – it's basic genomic studies. It doesn't need to classify – genomic studies are by definition genome wide and they include sequencing and array. So why not just change that second bullet point on the genetics to genomic studies?

DR. AMARAL: Okay.

DR. SANDERS: And then I think we add an equal bullet point, which is the same for both genetic and environment, which is application of (Omic) technologies to – what? To identify risk factors.

DR. AMARAL: You're saying that would go in the third section?

DR. SANDERS: No, that would go in both the first and second section.

DR. AMARAL: I see.

DR. SANDERS: Application of (Omic) technologies and we could even spell out transcriptome, epigenome, proteome, metabolome to identify risk factors. So identify and interpret risk factors – how does that sound?

DR. AMARAL: How do people respond to that?

(No response.)

DR. SANDERS: Is that a good silence or a bad silence?

DR. HERTZ-PICCIOTTO: I'm sorry, every time I go off mute I have to – my iPhone is not letting me get back on. I have to enter my whole passcode and all of that – sorry. So I just wanted to ask the question of whether the outline would do well to have a fourth category – we haven't really gotten to that third category, but I feel as if there are – there's a lot about this use of (Omic) technologies and general mechanistic, you know, all the range of kinds of mechanistic work that involves, you know, multiple organ systems – whether it's the immune system or whether it's the GI system or whether it's the hormone systems, endocrine systems that may or may not link between genes and environment, but are really critical to understanding etiology.

And that maybe it would be helpful to have that as its own piece and then highlight very specifically what we see the linkage of gene by environment and all the different types of gene by environments interactions that, you know, that will help to make those linkages and help us understand in a really broad sense – a more comprehensive sense – how factors combine together to cause autism. So, anyway, that's my proposal and I know I'm kind of jumping ahead a little because we hadn't really started into that third category, but I felt like some of the things there belong as mechanisms for understanding path of (unintelligible) and will help us understand

upstream risk factors, whether it's environmental or genetic.

DR. LAWLER: This is Cindy – one of the things I remember we discussed at the last IACC meeting is this kind of boundary issue between chapter and, Susan, you can remind me of what the resolution was, but I think what Irva is describing is almost, you know, how to re-bridge the work under this chapter with, you know, the previous – the question 2 that has to do with kind of underlying – understanding the biology of autism. So, I mean, maybe some of what you're describing, Irva, could be part of the section that does try to connect the work here with other parts of the plan.

DR. DANIELS: Sure, you could do that. Question 2 – I've tried to keep people away from getting too much into the underlying biology of causation because that's what this chapter is about, but they're kind of talking about path of physiology throughout the lifespan and various mechanisms and, you know, whether it's looking at animal studies or clinical studies or whatever in question 2. And so I think anything that is really getting at causation is fair game for this chapter and if you want to say something that links the two, I think that's fine.

DR. AMARAL: Can we – I just want to go back to Stephan's suggestion.

DR. DANIELS: Yes.

DR. AMARAL: Which I want to second because I think it actually clarifies – so I think what he had said was that we (unintelligible) genomic studies in section 1, but then the use of strategies for understanding risk factors. We already – you know, we talked about (unintelligible), but you know, looking at epigenetic factors and things like that could fit into that second section too. So I just wondered whether people are comfortable with that

suggestion just because we're going to need to clarify this if we're going to be able write this section in an orderly fashion. So does anybody have any concerns about that change to the outline?

(No response.)

DR. AMARAL: It doesn't – maybe not.

DR. HSIAO: This is Elaine Hsiao. I just wanted to also, I guess, third that. I think it's going to be very important to integrate the (Omic) surveys alongside the genetic study. And it kind of touches on the previous comment about integrating potential contributions of different organ systems. And so I think that it's in line with that integrative biology – understanding underlying autism. So, yes, I just wanted to say I also agree it's important.

DR. DANIELS: So this is (Susan). The question I have for you, with the previous comment that talked about maybe having a fourth section. Do you think that – does the group think that you would like to have two different sections – one that's really genes and environment and one that's about these other organ systems and, you know, the endocrine system, the immune system – whatever. All of that separately or do you think that it all fits together in looking at the full context of genes and environment?

DR. HSIAO: This is Elaine again. I think that they do fit within the bounds of section 3. I guess section 3 currently eludes to immune pathways, but integrating other organ systems as well I think would important in understanding gene environment risk.

DR. SANDERS: I think I agree. I think they work well in a single category. I think the immune system is a good example. So if you take the microglyial finding of Dan Geschwind and (Don Arking in the post-mortem brain, it's very

(unintelligible) with other genetics – led by genetics, led by environment or it's even causal. The way it's written at the moment I think that fits nicely in here and the identification of a potential causal factor then sends you down this route to try and understand how it gets there and that's (unintelligible) thinking about those (unintelligible) environment. The alternative – we just split out complex systems, but I think it's very hard to draw a clear line of what you mean by complex system. (Unintelligible) something as simple as sign ups.

DR. DANIELS: I think when – this is (Susan) – I think when the group was discussing it before with complex systems, they were just talking about the interactions of all of these different aspects – the different organ systems, genetics, the environment – all of that together and how they influence each other.

DR. SANDERS: So maybe complex systems doesn't quite capture that. Maybe it's understanding multi-variant risks?

DR. DANIELS: Very good. Thank you. So I guess – did we finish with the section 2? Was there anything else anyone wanted to offer for that?

DR. LAWLER: This is Cindy chiming in again and I'm wondering – we've got a bullet about risk communication under genetics and whether we want to think about, you know, sort of public health implications and, you know, kind of risk communication also in the context of the exposure section.

DR. SANDERS: Yes, absolutely.

DR. AMARAL: Yes, I agree.

DR. DANIELS: Okay, we can add that.

DR. SANDERS: And similarly, what about exposure testing? I mean I don't think…

DR. DANIELS: As the comparison to genetic testing?

DR. SANDERS: Absolutely.

DR. DANIELS: Unintelligible) exposure for individual?

DR. SANDERS: Yes.

DR. DANIELS: Is that science you want to see happen in the future? Are we really doing that now?

DR. SANDERS: I think it's very aspirational at the moment, but maybe this section would simply say about (unintelligible). I don't know.

DR. HERTZ-PICCIOTTO: I mean one of the things about the testing is it sort of builds – it seems to be predicated on the idea that it's deterministic or very close deterministic to be able to really, you know, as opposed to a risk score approach and so I think if you're talking about risk scores where, you know, people can – would get a number that puts them kind of on a continuum, you know, that to me – you know, has potential both on the environmental and the genetic side. I think the – but, again, it's very – we're so far from that and we have so little understanding of the mitigating factors that happen with regard to virtually any of our environmental risk factors that aspirational – I don't know if it belongs in this chapter really. What caused this to happen? Isn't there another chapter that has to do with sort of a prognostic kind of…

DR. DANIELS: There's one that's on diagnosis and screening, but not really prognostic.

DR. HERTZ-PICCIOTTO: Yes, well screening – so screening. I think if the testing we're talking about is – yes, what kind of testing are people

talking about? Are they talking about screening tests?

DR. LAWLER: Yes, I'm not – I wasn't thinking of testing. I was thinking more on, you know, how do you communicate, what are things you can talk to pregnant mothers about that, you know, probably nothing is going to be – no action is going to be specific to, you know, reducing autism risk, but there are, you know, certain public health messages that I think, you know, we can continue to put out there, you know, as the science continues to advance. But just leaving that out because, you know, we don't have the specificity and we're not quite sure. I think does disservice.

DR. SCHIEVE: Hi, this is Laura. I would really agree with that and I agree that we're really not there yet, but I think that we should be mindful of that – that that's what the public wants and that's where we should be headed in terms of thinking through these risk factors. So I think giving parity to that between the genetic and environmental risk factors is important. Because I do think that's the majority of questions that we get here is what's my risk if I do this and I think at least acknowledging even that there's a long way to go to understand that and what goes into that is important and so that researchers going forward can also be mindful considering that question in their studies. Even if it's not really answerable at this point or from any one study.

DR. DANIELS: Good. Anything else for the second section before we move on to the third section? So to talk about the third section, I just want to be mindful of our time so you have enough time to talk about your objectives. We have elucidate linkages between genes and environment and we also discussed understanding how genes and environment contribute toe phenotype is maybe a different way to word that that might be a little broader.

So in this section we listed some topics we discussed last time, which include gene environment studies and rewording complex systems to understanding multi-variant risk. Impact of environmental exposures on diverse populations and, I guess, diverse genetic backgrounds, animal models, epigenetics, microbiome, metabolomics was mentioned here, immune system, endocrine system, the need for a multi-disciplinary workforce and approaches and data access and data sharing. Are there some – is there something that you want to discuss here – things that you think are missed or need to be reworded or redefined?

DR. AMARAL: Susan this is (David) – so I think what you've heard in the last discussion was, you know, the tension between genetic studies and environmental studies. And so I think it's a little too glib to put gene environment studies because I think – actually at this point there still is a huge missed opportunity. There are, you know, for example, two very large whole genome sequencing – or whole (unintelligible) sequencing studies going on and I may be wrong, but I think that there's very little environmental data that's being collected in association with that. And probably the same is true for bigger environmental studies that aren't, you know, linking – doing whole genome sequencing.

So I think rather than just saying gene environment studies, you know, we have to sort of emphasize the fact that we need to capitalize on existing studies to forge a real linkage between genetic studies and environmental studies. And that sort of plays into this idea of looking at multi-variant risks. It's probably not going to be one or the other and until we start to really seriously looking at both at the same time, you know, we're going to be spinning our wheels I think.

DR. HALLADAY: Well I mean is that – (David), this is (Alycia) – is that something at least worthy of, you know, making mention in this

document of the types of studies that should be – that should, you know, go anew and then also utilize the data sets that are already out there?

DR. AMARAL: Yes, I think so.

DR. LAWLER: I mean I agree with what you just said. But – (David), what – so how would you change that first bullet to make that clearer? So you're talking about, you know, sort of encouraging studies that are, you know, looking at joint evacs or adding an exposure component to a genetic study or vice versa? How would you – how could we change that to give that flavor?

DR. AMARAL: Yes, so I think it would have to be something more like enlarged genetic environmental studies – or I don't know if motivating is the right word, but, you know, it's not that there aren't big studies going on. It's just that they're being done independently. So maybe other people have better suggestions for how to phrase this, but I really do think that the document should be saying that a missed opportunity and a need is to really facilitate that kind of interaction in the future.

DR. SANDERS: I think there's two actions here. I think that one of them is trying to take combined Omic approaches, which combined based in a gene environment. I think there's also a very specific focus on the gene environment's interaction. So, for example, if you found a gene which had a very clear link to a very – to an obvious environmental factor, you'd want to focus in on that. So I think it's similar to the environmental question – to capture both the Omic approach and also the sort of specific targeted hypothesis. But I agree that both are important.

DR. HERTZ-PICCIOTTO: So in terms of what would make this happen, I've thought about this a lot. And I mean I think other people on this call have too. And, you know, for example, you know, - (Alycia), - you promoted this – the development of

the ELEAT tool, the environmental life exposure assessment tool. And I think the – one of the ideas of that – of having that tool was that this could be something that could be relatively easily incorporated into genetic studies widely and would thereby produce these amazing datasets that we'd like to see, which would have a lot of exposure data.

Admittedly all of that was focused on just, you know, reported questionnaire type of data, but it would be – still put us quite a ways forward from where we are today. And – but, you know, I think another component of this is that when the funding agencies require, you know, or put out calls that enable these kinds of combined approaches, that's when the researchers respond.

And so, you know, some of it really is in the hands of the funding agencies to offer those opportunities that will get people talking to each other who haven't been talking to each other. And, you know, I think there can continue to be this sort of smaller studies. There haven't been too many. I mean we've published three of them showing some pretty strong specific gene by environment interactions in the sense of the synergy where the combined effect is much greater and sometimes is there even though the factor – one of the factors alone, you know, does not show up. For instance, the folic acid metabolizing genes that really have no impact whatsoever, except in those people who don't take the prenatal vitamin supplements early in pregnancy where you start seeing these very very high relative risks for those who have the inefficient metabolizing genes – or the inefficient transmethylation genotype and did not take the prenatal supplement.

So there's certainly lots and lots of opportunities and many pathways that can be explored in that type of way outside of the exposome approaches. And then with added technologies that can allow us to characterize, you know, hundreds and thousands of analytes in

drop of blood or a piece of dust or, you know, some urine. It can be a lot more powerful and, you know, it's starting to happen. So we've – but it does need to be happening in a faster pace with the – and could be promoted with, you know, funding opportunities I think that focus on that sort of thing.

DR. SANDERS: How about we change the text to say, studies which assay boosted genetic and environmental exposure?

(Pause.)

DR. AMARAL: That sounds…

DR. HALLADAY: I like where that's going – this is Alycia. I like where that's going.

DR. AMARAL: Yes.

DR. HERTZ-PICCIOTTO: I think we could use the word leveraging. I think leverage kind of really captures it.

DR. AMARAL: That's a good word. I like that.

DR. SANDERS: Two other bullet points stand out to me. Animal models should change to model systems to embrace (IPSL)s and I think epigenetics standing on its own seems strange. It should be epigenetics, transcriptomics, proteomics, metabolomics.

DR. AMARAL: Yes, I agree with both of those. Does the other – the other comment is the diverse populations bullet just limited to environmental exposures seems a little…

DR. SANDERS: Yes, I thought that, but I guess diverse populations sort of captures sort of genetic background, which we expect to be the main genetic contributor.

DR. AMARAL: But isn't there something about we want to have more diversity in our genetic studies as well?

DR. SANDERS: Yes, that's true.

DR. AMARAL: So, I mean, I think I would broaden that a little bit more. I mean I think if it stays here because it doesn't have another logical home that makes sense, but…

DR. SANDERS: Yes.

DR. LAWLER: I think that's made clear in the overall – one of the overall objectives. That the first objective – so I agree, clarifying it here to make sure that it applies to both exposure, focus studies and genetic studies would be helpful.

DR. SANDERS: Yes.

DR. AMARAL: I wonder whether – I was also going to raise the (IPSC)s and I wonder – should that be a separate category given that they're actually not necessarily modeling a human condition. They are a human condition whereas the animal models and (unintelligible) models are simulations.

DR. SANDERS: I think based on limitations. I mean so you could argue that (unintelligible) at least you have an intact working brain with a stem cell you're stuck with a cell or a mini-brain. I think both are models which have this question to how relevant you are to the human reality.

DR. AMARAL: That's fine.

DR. DANIELS: All right, anything else for this section? So I think you've had a good discussion and, you know, we'll make some updates to this outline and then share it back with you. And, of course, this is just the outline just to give you hints at what you're going to be writing about. So

we just want to make sure that we include all the topics that you think are important. I think we actually added quite a lot on today's call. So that's great.

So then I'd like to move on to talking about objectives. So our team here in the office just looked back at what we discussed on previous calls and we came up with three draft objectives based on what you discussed, but you can feel free to suggest changes, totally alternative objectives or rewording of what you see here. So just to go over these draft ones that we're here just to get your conversation started. The first one is strengthening the understanding of genetic risk factors for (ASD) across a large population representing the full diversity and heterogeneity of those with ASD.

The second is understand the effects of ASD risk on individual and multiple exposures in both the prenatal and post-natal environment over time enabling development of strategies for reducing severe disability and co-morbidities in ASD. And, third, expanding knowledge about functional linkages and complex relationships between environmental risk factors and specific biological mechanisms that may be involved in ASD, such as altered gene expression or immune pathways, which might be a little bit simplistic, but in developing these objectives we want them to be distinct from other so that there's no a lot of overlap between them. Because that will help us when we're later looking at the portfolio to see what research has been funded that might be related to these as well as, you know, in some cases service projects not as much for this chapter. But it helps us if they don't overlap significantly.

So what do you think about these? Do you have suggestions for any alternates or rewording?

DR. SANDERS: So the section in 2, enabling (unintelligible) strategy through reducing severe

disability and co-morbidities in ASD – two thoughts. Firstly, I'm not sure why the word severe is in there. I think any form of disability and co-morbidity is worth trying to improve. And, secondly, it's not clear to me why that's only included in the environmental (unintelligible). Because I think it's the ultimate goal in the genetics to, but then again you just made the point about trying to make them distinct. I'm not quite sure how to solve that.

DR. AMARAL: Yes…

DR. DANIELS: No, I think what we did was we tried to come up with something that was really related to the genetics aspect, something that was related to the environment and something that was combining all of them, which was just one approach and you can feel free to change that if you want, but that was one way of keeping them distinct. But, you know, we're open to other suggestions. In terms of severe disability, it's – the reason that wording has come up in the strategic plan a few times is I think with some members of the community they feel if you talk about reducing all disability that you might be trying to eliminate their positive features, which some of their disabilities they don't feel are severe enough that you would want to be rid of them or to not have them – if that makes any sense.

DR. AMARAL: Susan, I feel (unintelligible). I don't (unintelligible) makes sense – this is (David) and, you know, disability is a disability – right?

DR. SANDERS: Yes, exactly.

DR. AMARAL: It's on a spectrum and I think you, you know – I don't think we need to add severe there and I think it would perfectly appropriate. And I also agree with Stephan that, you know, developing strategies for reducing disability and co-morbidities is an appropriate goal for the genetic risk factors as well. So I

think, you know, to have that balance actually makes more sense than to try and distinguish it in that way. It's still distinguished on environment versus genetic and I think, you know, that will be enough to give you direction as to which studies go into which bin.

DR. DANIELS: So to repeat that – so, okay, we could get rid of the word severe, but what else do you have to suggest for number 2 to reword?

DR. AMARAL: I think – just enabling development of strategies for reducing disability in co-morbidities can also be put into item number 1.

DR. DANIELS: Oh I see, okay.

DR. SANDERS: Yes, exactly. I think there was a recognition it might be a little bit easier to modify exposure than genetics, but I think that's a good way of putting it.

DR. DANIELS: All right. Other thoughts about these?

DR. SANDERS: The other thought I have was that three, I think, implies the idea that environment doesn't act through ha biological mechanism. So I think it's trying to do the same (unintelligible) essentially combine gene environment to understand how the actual biological mechanisms. So maybe, expand the knowledge of how multiple genetic and environment risk factors conspire in specific biological mechanisms. And I'm not sure there's any need to highlight gene expression or immune pathways.

DR. DANIELS: Yes.

DR. SANDERS: I think it follows that any risk factor needs to act through gene expression. It's just possible it wouldn't need to, but I think highlighting it is probably – we're probably not there yet.

DR. DANIELS: Fine. Other thoughts? So with those changes, does the group feel like they would be happy with these objectives?

DR. AMARAL: So can you read what the item 3 now is?

DR. DANIELS: So I wasn't sure about the word conspire – I don't know.

DR. SANDERS: Yes, it sounds a bit (unintelligible).

DR. DANIELS: That might, you know, not be the perfect word to choose there, but expand knowledge about how multiple environmental and genetic risk factors act together through specific biological mechanisms to – I don't know – create ASD phenotypes or something like that. I don't know what…

DR. SANDERS: Yes, to (unintelligible) the ASD phenotype?

DR. DANIELS: Yes. Yes, that would be good.

UNKNOWN FEMALE SPEAKER: What was that word? I didn't catch that.

DR. SANDERS: Lead to.

UNKNOWN FEMALE SPEAKER:I was going to say influence, yes.

DR. SANDERS: That's good too.

UNKNOWN FEMALE SPEAKER: That's fine.

DR. AMARAL: Yes, so that's emphasizing the interaction between (unintelligible). Right?

DR. DANIELS: Right.

DR. AMARAL: I mean that's…

DR. DANIELS: Right.

DR. AMARAL: Yes.

DR. DANIELS: And then the first one we would just be adding enabling development of strategies for reducing disability and co-morbidities in ASD and then the second one would stay pretty much the same, but without the word severe.

DR. AMARAL: Yes.

Dr. DANIELS: Okay, that's great. So I think if the group is happy with those then we can just make those changes. So I wanted to talk with you next about the aspirational goal. On the last call the working group proposed that we add diagnosis into the aspirational goals. So the aspirational goal is just an overall statement of where you think this field needs to be leading. And so the aspirational goal now would read causes of ASD will be discovered that inform diagnosis, prognosis and treatments that lead to prevention or preemption of the challenges and disabilities of ASD. And I don't know if you want to add anything about co-morbidities. That was one other aspect.

DR. AMARAL: I think you need to because the co-morbidities are one of the challenges of ASD.

DR. DANIELS: So then we can put that in there. With those couple of small changes, do you feel like that reflects your current thinking about the direction of the field?

DR. AMARAL: I was saying, (Susan), that you don't need to add co-morbidities.

DR. DANIELS: That we don't need to? Okay. So it will be just challenges and disabilities of ASD. So it's just really adding the word diagnosis in with prognosis and treatments. And then on the title, what caused this to happen and can it be prevented? On the last call it didn't sound like

the group wanted to make any changes, but I just wanted to give you one more chance to consider that if you have any suggestions.

DR. SANDERS: I have one thought on the aspirational goal – it's going to be controversial. Do we want to add something along the lines of while it's recognizing that there may be positive aspects to the ASD trait?

DR. AMARAL: Stephan, we've talked about actually having a section at the beginning of this chapter where we would discuss the fact that, you know, there are many aspects of autism that you wouldn't want to prevent or treat.

DR. SANDERS: Right.

DR. AMARAL: So I think if you put it into the aspirational goal, you know, it defuses – you know, it may just distort the real effort.

DR. SANDERS: Yes, great.

DR. DANIELS: Yes, so we'll add that to the outline, David. That was something that you did discuss last time that we didn't have it in the outline. We'll make sure that that's a part of it to prompt you on writing that introductory.

DR. AMARAL: Yes, at least sort of a preface to it.

DR. DANIELS: Yes, so we've made it through all of the points that we need to discuss on this call. Are there any other questions or thoughts you want to share before we conclude?

DR. LAWLER: Yes, this is (Cindy). I may have missed it, but was the group consensus to leave the title (unintelligible).

DR. DANIELS: Oh, so I didn't hear anything so I was assuming, but does anyone have anything else they'd like to say about the title? So the title

is supposed to reflect a consumer based question that they might have about causation. And so what the original IACC came up with was what caused this to happen and can it be prevented?

DR. SCHIEVE: This is (Laura). I think the title is fine, but now that the it is not what's being prevented as much as the challenges and disabilities, which I agree is the correct direction to go, I'm wondering if that should be modified at all. (Unintelligible) to modify it is it becomes much more complicated and less public friendly.

DR. DANIELS: Yes, so do you have a suggestion? Like something about reducing challenges and disabilities or something along those lines?

DR. SCHIEVE: Well, yes, I guess it would be can disabilities – or can the challenges – can the disabilities associated with autism be prevented or the level of disability perhaps, but I'm not sure that quite gets it either. I need to think about it a little. I don't know if other people have thoughts on that, but it seems like it's a little bit of a mismatch now since the aspirational goal is moving in a very specific direction.

DR. LAWLER: This is (Cindy) and I agree with don't like the way it is worded now because the it – I mean that word prevention and that does suggest that we, you know, are aspiring the prevent autism and maybe we do need to go with a more wordy title.

DR. DANIELS: (Unintelligible).

DR. LAWLER: Go ahead.

DR. DANIELS: Going into your aspirational goal you could say, what caused this to happen and can we preempt the challenges and disabilities of ASD or something like that.

DR. LAWLER: Yes.

DR. AMARAL: So…

DR. LAWLER: Just repeat that same language.

DR. SANDERS: So….

DR. SCHIEVE: And I was going to suggest what caused these problems to happen and maybe that could be combined with what – with the suggestion that was just made.

DR. AMARAL: (Unintelligible) view – I actually like this – that the statement. And what caused this to happen and can it is the cause. Right? (Unintelligible) and so I think that this really captures the environmental, the genetic – all the aspects that we talked about and it's the disabilities. It's what that caused it. It's, you know, it's the factors that we've been discussing on the entire call. So I mean, you know, and actually a little bit of ambiguity in it is probably good, but I really do think that it (unintelligible).

DR. SANDERS: Can we change preventative to modify?

DR. AMARAL: Say again?

DR. SANDERS: Can you change the word preventative to modified?

DR. AMARAL: You know, I think – again, if it's a consumer oriented statement (unintelligible) consumers that would want to see if modified (unintelligible).

DR. LAWLER: (Laura), can you go back and…

DR. DANIELS: I'm getting some background noise.

DR. LAWLER: (Unintelligible). Can you restate that?

DR. SCHIEVE: I'm sorry, I didn't hear what you said.

DR. LAWLER: I'm just trying to remember what your proposal was. What caused it to happen and can…

DR. SCHIEVE: Oh, yes – right, when I read this, I read the it as the this rather than the cause.

DR. LAWLER: Yes.

DR. SCHIEVE: And so I was thinking the it be substituted with either challenges in disabilities or disabilities or the level of disability were the three things – but I was trying to keep the wording – some of the same and I don't know if it's helpful to do minimal as possible changes to the title so that it is – so that it is recognizable – the progression of it from past strategic plans or if that doesn't matter at all.

DR. DANIELS: I think that – this is (Susan) – substituting challenges and disabilities for it would work, but the original committee – I think what they meant by the it was can autism be prevented. Just because this was back in 2007 when they were coming up with this and at the time that was kind of where they were going with it and I think that that was evolved a lot in the last few years. So I think having some clarity about what you mean by it would be helpful.

So if you added challenges and disabilities in there that wouldn't add too many words.

DR. AMARAL: How about just adding disability then if that's…

DR. DANIELS: Or disability – can disabilities be prevented or disability be prevented? Do we like…

DR. SCHIEVE: Maybe the disabilities?

DR. DANIELS: Do you want prevented or reduced? That would be another option.

DR. AMARAL: Let's aim high.

DR. DANIELS: Okay. And, of course, you know the IACC will look at this as well and provide their feedback. So all of the objectives that you've come up with and then what you write will be looked at by the committee and they'll be able to provide their input on this as well.

DR. LAWLER: I mean any of this – the recent suggestions are better than the current title. So, you know, I don't have strong feelings either way, but I would be comfortable with any of those.

DR. DANIELS: So why don't we go with disability be prevented for now and then see how the committee likes that and if they have any other suggestions.

DR. HERTZ-PICCIOTTO: Can I also make a – okay, actually…

DR. DANIELS: Go ahead – I mean if you have a different suggestion.

DR HERTZ-PICCIOTTO: (Unintelligible) aspirational goal – not for the title. I feel like we've gone around this a few times on that, but – so maybe finish talking about that and then I want to go back to the aspirational goal. I had had to close down my computer, but now I'm looking at – I have something I wanted to say about that.

DR. DANIELS: Okay, go ahead.

DR. HERTZ-PICCIOTTO: Oh okay, so I would like it to say – so how is it now changed?

DR. DANIELS: So it says causes of ASD will be discovered that inform diagnosis, prognosis in treatments that lead to prevention or preemption of the challenges and disabilities of ASD.

DR. HERTZ-PICCIOTTO: So I would say that that change doesn't quite work because diagnosis, prognosis and treatment do not necessarily lead to prevention. I think when, especially when we're talking about sort of these, you know, very extreme kinds of causes, I would make it two clauses as it was originally written where we'll be discovered that inform those things and will enable prevention – preemption of the challenges and disabilities.

DR. DANIELS: Yes – sorry, I don't know what I said when I was reading it. It does say and – it doesn't say that. So that…

DR. HERTZ-PICCIOTTO: Okay and I would prefer something like will enable rather than will lead to. It won't automatically lead to, but it will enable us to identify those strategies of prevention and preemption.

DR. AMARAL: I think it's more straight forward, Irva, if you just say and lead to prevention. I mean, you know, it's a trajectory towards it. So it encompasses enable – right?

DR. LAWLER: And it's an aspirational goal. So you have to…

DR. HERTZ-PICCIOTTO: Okay. All right, as long as its and and not (unintelligible).

DR. DANIELS: It is and. So I'm not sure what I said, but it is and.

DR. HERTZ-PICCIOTTO: Okay, that's fine. All right.

DR. AMARAL: Yes, so that's good to clarify it.

DR. DANIELS: Yes, so that's good. Any other closing thoughts?

DR. SANDERS: (Unintelligible) comment, but the capitalization of the title seems quite strange. (Unintelligible).

DR. DANIELS: Oh, that was just a format that has been used in the plan. So just to make it more like a title.

DR. AMARAL: I just wanted to thank your team for organizing all of this. You know, it's really a lot of work to try and integrate all of the comments that you get over the first to calls and come up with this nice scheme. So it's made it sort of easy for us to address the main points and any concerns that we have. So thanks to your team for doing that.

DR. LAWLER: Yes, I'll echo that. This was probably about as seamless as it could have been and I really – I think it took capitalizes on, you know, busy schedules of the investigators that are a part of this team and they'll be more willing to do these kinds of things in the future because you've really kind of laid the ground work and produced these nice summaries that – and I know it's a tremendous amount of work, (Susan), so thank you very much.

DR. DANIELS: Yes and thank you to our team here. We appreciate the acknowledgement and our goal is to make this as easy as possible and to be able to get all of our valuable input for this process. So we appreciate your participation. Excuse me.

So what we will be doing next is we're going to try to incorporate all the feedback that we got on the outline into the outline and update the objectives and the aspirational goal and title and then get that information back to the chairs. We

can have a discussion with the chairs ahead of time and then we'll be looking for volunteers to help write certain sections and if any of the working group members already know that you'd like to contribute to certain sections, feel free to send me an email or send something to (Cindy), (David) and me to let us know.

And – otherwise I'm sure that the chairs will be tapping you to ask you for some help in areas of your expertise and we are going to try to set a goal to have some kind of a draft available before the (IACC) meeting that is happening on January 13 – I don't know why I wanted to say July – on January 13. And so we will be definitely going over all of the objectives and we'll provide them with whatever you have available in writing. I know that the holidays are coming up and so it might be a little bit tight, but whatever you are able to get together before the meeting I'm sure will be appreciated by the committee and they very much appreciate the input of all the working group members into this process.

DR. LAWLER: (Susan), can you just briefly remind us of what are the writing tasks? I mean there's that background section and then – I mean…

DR. DANIELS: So, yes, so what we're going to do is we're taking this outline and going to flesh it out into some more verbiage to describe what have been some major advances that have been made in the field that have changed the field and then what do we need to do next – what are some of the barriers and challenges that we're facing. Just to give context before you get into those objectives and you would – I'm asking each working group to do something under 10 pages – or 10 pages or less.

To try to keep them, you know, short but I know that there's a lot to say and so I thought 10 pages was a reasonable starting point and, you know, if it turns out to be a lot shorter than that then that's fine and if, you know, you're reaching your limit of 10 we'll just try to keep

the entire strategic plan to – if we just did that it would probably be around 80 pages, which is kind of long, but it's also going to be meaty hopefully and informative for the public. And to keep in mind that we want to write in a lay friendly format so that a family member of a person with autism or a person on the autism spectrum could read this and understand what we're discussing. So does that answer your question?

DR. LAWLER: Yes, that's helpful.

DR. DANIELS: Great. So we'll start with an outline and then with the chairs you can look through that outline and help determine who on the working (unintelligible) contribute to various sections or if you wanted to yourself try to put something together and then give it off to somebody who is – has expertise in that field to try to put some input and polishing to get together some language that we can use to describe the progress and challenges and future directions in the field that the committee would like to see happen.

DR. AMARAL: (Cindy), maybe once we get the edited outline we can have a phone call offline to go through it and see who wants to do what. What do you think?

DR. LAWLER: Yes – no, I think that sounds good.

DR. AMARAL: Okay, all right. We can set that up offline.

DR. LAWLER: Okay.

DR. DANIELS: That sounds good. And well thank you all for your participation and we will be in touch.

DR. SANDERS: Okay, thank you.

DR. AMARAL: Thank you, (Susan).

DR. LAWLER: Thank you.

DR. AMARAL: Bye bye.

GROUP: Bye.

(Whereupon, the conference call was adjourned.)