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STRATEGIC PLAN UPDATE

Working Group 3 – Question 3 – What Caused this to Happen and Can It Be Prevented?

Conference Call 2

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PROCEEDINGS:

DR. SUSAN DANIELS: Thank you and welcome to today's conference call -- the second conference call of the IACC's Strategic Plan Update Working Group 3 on the "Strategic Plan Question 3 - "What Caused This to Happen and Can It Be Prevented?" That's about environmental and genetic risk factors for Autism spectrum disorder. I'd like to welcome our public audience. And for members who are listening online they – you can find all the materials for today's call on our web site at the IACC web site. And thank you to the Working Group members and to our co-chairs, David Amaral and Cindy Lawler for joining us today.

So I'd like to first do a roll call to let everyone know who's on the phone. And after I read your name if you could just say one or two sentences about the (unintelligible) and how you relate to the group here. Let's start with David Amaral.

DR. DAVID AMARAL: Hey. So it's Director of the Mind Institute at UC Davis. I'm a neuroscientist and have been carrying out longitudinal studies of, you know, typical characteristics of Autism.

DR. DANIELS: Thank you. Cindy Lawler?

DR. CINDY LAWLER: Hi. I'm the Chief of Genes Environment and Health Branch in Extramarital Division at the National Institute of Environmental Health Sciences and I manage a portfolio of research that's focused on understanding the contribution of environment in the context of genetics susceptibility as well.

DR. SUSAN DANIELS: Thank you. Ruth Etzel?

DR. RUTH ETZEL: Hi. I'm the Director of the Office of Children's Health Protection at the Environmental Protection Agency.

DR. DANIELS: Thank you. And the first three people here who have introduced themselves -- David and Ruth -- are members of the IACC and Cindy is an alternate on the IACC. So then I'll move to the others on the call. Rafael Bernier?

DR. RAFAEL BERNIER: Yes, hi. I'm a Professor at the University of Washington here in Seattle. I'm also the Clinical Director of the Seattle Children's Autism Center and my research focuses on assessment and characterization of individuals with Autism as part of a number of different genetics to Autism.

DR. DANIELS: Thank you. Evan Eichler? Danielle Fallin is not going to be on the call today. And Dan Geschwind is not going to be on the call today. Alycia Halladay?

DR. ALYCIA HALLADAY: Hi. I'm Alycia Halladay. I'm the Chief Science Officer at the Autism Science Foundation.

DR. DANIELS: Thank you. Irva Hertz-Picciotto.

DR. IRVA HERTZ-PICCIOTTO: Hi. I'm the Director of the Environmental Health Sciences Center at the UC Davis and faculty member of the Minds Institute and Director of a program on environmental epidemiology of Autism and new development.

DR. DANIELS: Thank you. Elaine Hsiao?

DR. ELAINE HSIAO: Hi. I'm an assistant professor at UCLA. I study animal models of environmental risk factors for Autism including maternal immune activation and microbiome contributions.

DR. DANIELS: Thank you. Craig Newschaffer? Elise Robinson is not going to be on the call today. Stefan Sanders? And Joan Scott?

MS. JOAN SCOTT: Hi. I'm Deputy Director in the Division of Services for Children with Special Health Needs in the Bureau of Maternal and Child health at HRSA where we provide programming support around Autism mainly in the services area, but I also come – also have a genetics background.

DR. DANIELS: Thank you. So - oh, is there somebody else who just joined us? Okay, well, thank you. So we've gone over the people on the Working Group who are on the call…

DR. CRAIG NEWSCHAFFER: Hi Susan. This is Craig.

DR. DANIELS: Oh, hi.

DR. NEWSCHAFFER: I was on mute before. Apologies.

DR. DANIELS: Thanks for letting me know you're on the call. Welcome. And do you want to say a couple of words about yourself?

DR. NEWSCHAFFER: Yes, I direct the AJ Autism Institute at Drexel University in Philadelphia. My research focuses on modifiable Autism risk factors.

DR. DANIELS: Thank you. So then we're going to start in on our first agenda item here. I have follow-up from call one. So on the last conference call we spent time talking about the 2013 portfolio analysis that my office did to look at the portfolio of research that was funded in 2013 and see if it had any information that was useful for you in terms of assessing what the state of funding is in this field so there was much discussion and we took some notes on that.

The follow-up we had was that there were some concerns that - of sub-category of research that the office put together that there was a subcategory analysis that in the gene environment

subcategory -- which is broadly just a bucket for all projects that did not fit into strictly genetic research, strictly environmental research, or strictly of the genetic research, but had elements of all of those - some or all of those in it -- fit into that category and that there were concerns that - about whether that was – those projects were accurately coded, etc..

Our team went back and looked at them. According to our definitions, they were accurately coded and there's been some discussion about whether for the purposes of the Working Group in the future we could break things down further and so there was some discussion about whether we should be pulling out gene by environment interaction type studies separately for the purposes of the Working Group and another possibility would be pulling out immune risk factor studies of a separate piece in the future for the purpose of the Working Group. So, you know, our office is willing to consider being able to provide that information that's helpful to the Working Group in terms of assessing the status of the field.

In order to do a gene by environment studies we would need a really clear definition that would make it very easy for us to be able to pull those separately from the other projects. So any particular thoughts there?

DR. HERTZ-PICCIOTTO: Yes, this is Irva Hertz-Picciotto. I got an - I was wanting to relate these questions and in just my familiarity with - in the ongoing literature I was really surprised to see a large – large room studies listed in that category so I actually went through each of the studies and read the abstract and came up with about around 17 or 18 of them that I had previous serious questions about what - either whether there was anything - any actual environmental factors that was going to be looked at whether there was any genetics that was being looked at

and whether it was both and it, you know, it appeared to me that that was – that there many that didn't so it – I'm not sure seeing that it might be helpful for most of us on the – this Work Group to find out?

And then you looked back and you had actually had the team go back and code them all again and came up with the same - the same one. So I'm just wondering if you could say anything more about the definition used and maybe we could talk about – I think it might not be that hard to come back with a viable and easily codeable definition, but it might be helpful to know a little more about what the definition was that your team was working with.

DR. DANIELS: So we had four subcategories that we used for this portfolio based on what we see as questions the public has. We often get it – asked, "How many, you know, what proportion of the portfolio is environmental research or looking at environmental risk factors?" so studies that were focused on environmental risk factors when – in that subcategory. We also get asked about what studies we have focusing on genetic risk factors and so if a study's on genetic risk factors that fits in that subcategory.

Epigenetics -- we had a number of studies that seemed to be, you know, a sizable number that we could put – have a whole subcategory devoted to epigenetics so we created that. And then the fourth was studies that may have elements of both genetic and environmental sub factor – risk factors together and various proportions not specifically gene by environment studies, per say, but including any kind of environmental risk factors -- not just chemical, but if it was infectious risk factors, environmental stressors, other, you know, nutritional supplement type risk factors – any of those types of risk factors could be there as long as there was also some component

of looking at a Geno type or a genetic background with it. So that's – it was a "catch all" place.

If we were to really focus it down to gene by environment studies, we would need to have something to call the rest of it and I'm hesitant to just create "other" because that's usually not informative for anyone. So if we had to have a separate subcategory we need it to be very clear and distinct. And so as we looked at…

DR. HERTZ-PICCIOTTO: Yes.

DR. DANIELS: …we saw that there are a number of projects now that involve immune risk factors and I think there's enough of them that that can be a subcategory, but again, what to do with the things that wouldn't fit into gene by environment if we have a narrow definition of that to make it so that they just don't get lost as "other".

DR. LAWLER: So this is Cindy. I – Susan I just wanted to thank you for the additional information that you provided around this after our last call. I think when I looked at the number of studies initially before that call I was a bit skeptical because perhaps like Irva, I had a better – well, a couple things -- one I was thinking of more in the gene by environment category and I was familiar with the products of some of the work and I knew the, you know, there were very few publications -- but the information you provided subsequently I think has clarified it for me.

I know that as a – it's not meant to only be gene by environment. I spent quite a bit of time going through the list and there are - in my mind, there are only really a few that I would (quibble) with. I would say less than half of the ones that Irva looked at and now, you know, in some cases I have a little bit more knowledge about the particular study than is just what's in the abstract so that might have – has helped me – I, you know, look some things up.

I don't want us to get distracted on this call so perhaps if we could come to some agreement or consensus about whether we want in going forward to flag studies that we think would reflect joint effects of genes in environment and we can work on that perhaps offline so that we can continue on the call today and really identify what kinds of progress that we see in the field because I think this other discussion is just going to end up burning up a lot of time and in my mind with the information you provided has really satisfied me for, you know, probably 90% Susan.

DR. HALLADAY: I wanted -- this is Alycia -- I want to also thank Susan for providing that clarification and I want to second -- I don't know if this is the process on these calls -- but second when Cindy said in that we need to kind of look forward. I don't know if this group has ever come up with a definition and I could be wrong if they have of what is a gene environment interaction. You know, specifically as we go forward, as the science has gone forward, as we think forward of the new, you know, versions of the strategic plan maybe that should be a priority as kind of putting the parameters over what that means.

DR. DANIELS: …being able to work on it offline would be a good idea and not to use up too much time on the call, but certainly, you know, we're open to trying to explore those definitions more and if even if it's not something that would enter the official report that we put together, we're always happy to tag things and pull them out for the purposes of working groups so they can better understand the data and so, you know, we're happy to work with you offline on that.

DR. HERTZ-PICCIOTTO: Well, I was…

DR. DANIELS: Was there another…

DR. HERTZ-PICCIOTTO: Yes, (unintelligible) - yes, I don't want to hold things back. I think, you know, clearly the task of figuring out, you know, what needs to be done is the important one. I do, I mean, I'd be happy to have this discussion online because I did go through them pretty carefully and would like to hear a little more -- maybe Cindy some "needles out", you know the ones that we differ on.

I'm just wondering also though whether it would be, you know, because, of course, of this high profile it's out in the public that the category just – it needs to be described really well and I see a lot of basic biology in the set of studies that I, you know, either there's no genetic such as no environments by even a broad definition and, you know, certainly there are questions to discuss, "When is the term - what is the internal age as that environment or is it in essence?" is everything that might be influenced by environment – environmental and that sort of meets the almost biological marker is environmental.

But I, you know, I think it's important in the sense of saying, "Okay, where are we now? What is the portfolio?" And, you know, I guess I - I'm not convinced that the list is actually, you know, more that it reports to be and whether, you know, if there were another category which was basic biology. I think that would probably clear up a lot of these, you know, certainly immunology and what – how does immunology end up in the environment category versus, you know, some of the other questions that are, you know, before the community and through the other working groups lately.

I, you know, I don't quite get it. But again, I don't want to hold things back, but I do see - you know, so many of these don't mention genes for don't mention any environmental, you know, risk factors that, you know? And when looking through I

know one of the first options on the agenda today is discussed public comment and, you know, there's many people to say environment, but many do give examples which I think are the broad categories that need to consider things like you know, infectious disease and nutrition for certain - I'm the first to say that environment is much broader than environmental chemicals and it's, you know, many are things, you know, risk factors is environments so…

DR. DANIELS: Well, great. Well, we'll take all of this into consideration and like I said we're happy to work with people offline to see if there's more that we can do to make this information helpful for the Working Group, but I don't want to take up more of our time on today's call because I know that you're going to have a lot to share in terms of progress being made in the field. If it's okay, I'd like to move onto the next topic which is to discuss the public comments -- so that was a good Segway for that -- the IECC collective public comments over the summer on the strategic plan question areas -- so we wanted to know feedback from public about what they think in terms of the most important areas of concern or questions that they have -- areas that they would like to see more research or in some cases services that relate to these areas -- and so we provided the actual text to the public comments online on our web site -- which can be found under the "Meetings" tab down to the bottom -- and we also provided a list of themes that we pulled out of the public comments -- which is provided here as a document for the materials.

So if you look through this list of themes, again, our team just went through all of the comments and put this into some broad categories. So we saw comments that were about having better – meeting better methods for testing the contributions of risk factors from multiple domains to better understand the risk of Autism, comments about the need for a more epigenetics

research, more genetics research, more research on the immune system, more research on maternal and prenatal factors, more – so far every – of course most things are more research on gene environment interactions, on concurring conditions or risks for concurring conditions, the microbiome, familial factors, environmental risk factors, and then we had some comments either saying that we need more research to understand the role of vaccines or less research or no research to understand the role of vaccines.

Some comments that endorse the priorities that are currently in the strategic plan and some comments that said that looking at environmental risk factors is not a priority or it is a priority. So those were some of the broad bins that we put things in, but we wanted you to have access to the actual comments themselves too and give you a chance to discuss what you heard from the public and highlight anything that stood out to you that we need to take into consideration as we're working on the strategic plan update. So, floor's open if anyone has comments?

DR. AMARAL: Hi Susan. This is David. And first - so I did read through the comments and I was very impressed by first of all the number of comments and, you know, how significant they were and I think as we write this chapter we're certainly going to go back to those comments and pick up on some – many of the themes that are there, but there were two comments I wanted to make.

One is that, you know, there's clearly an "elephant in the room" and that is going to affect everything that this committee and this chapter has and that is that as really the polarization in terms of the community and whether they think it's a valuable goal to look for risk factors in order to lead to prevention and, you know, they're - clearly there's a group that believe that that's a valid goal and something that should be pursued

and then what I saw in many of the comments was that particularly I assume from people that are on spectrum themselves that they thought that pursuing a goal to prevent Autism was, you know, not valid.

I, you know, I don't think that, you know, at this point there's no clear way to adjudicate between those two perspectives, but I do think that in the document that we need to make it clear that there isn't - there isn't a consensus in the Autism community about which perspective and I suspect, you know, from my own interactions with families that it's the families that have more seriously affected individuals that are, you know, more in line with the idea of finding preventions in those that are perhaps not as, you know, medically affected are less inclined to looking for preventions, but at least that's something that we should address in the document -- so that was one comment.

The other though is something that I didn't see any place in the comments -- and maybe it's not appropriate for this section -- but that is, you know, for issues about what can be done in terms to reduce the risk of Autism. And one of the issues that I think -- and it may come up later -- that has gotten a lot of attention is, you know, folic acid supplementation both prenatally and there are data that suggests that folic acid supplementation is going to reduce the risk of Autism.

But then -- and it's a pity that (Danny) isn't on the call today because data that they presented at (INFAR) this year suggested that higher levels of folate might actually be a risk factor. So if there's a question that I think should – needs to be resolved it's that one related to folic acid and, you know, what kind of advice that the IECC can provide to the community. But then also, "Is there anything else in terms of supplements or anything else that might be reducing risk and is

there enough research in things that the community can actually do to reduce risk?" and I didn't see that in the documents thus far.

DR. DANIELS: So David just to give a little bit of historical background on your first comment about whether risk factors should lead to prevention, the committee has discussed this in the past and it helps them in terms of coming up with the aspirational goal for this chapter which reads, "Causes of ASD will be discovered that informed prognosis and treatments that lead to prevention/ preemption of the challenges and disabilities of Autism spectrum disorder."

I think that the committee decided the place that they – the committee could meet on this was wanting to reduce the challenges and disabilities of Autism, but did not specifically say, "prevent Autism in itself," but that was the past versions of the committee that kind of went there and that's something that's going to be open, of course, for discussion on today's call -- so thanks for bringing that up.

DR. AMARAL: Thanks.

DR. HSAIO: Hi, this is Elaine. I actually have a question about this document. Unfortunately, haven't gone through all of the public comments yet, but I wonder if you have a metric that will wait or prioritize these different points on the document. For example, you mentioned that some people expressed the need for more research on vaccines and others less research and so if there's a weighted version to see what the relative frequency of those types of comments would – were, that would be useful.

DR. DANIELS: So this is Susan and to just to respond to that. We actually went out of our way to not make this about numbers because it can be kind of distorting to say that, you know, there were a 100 of these and there's only one of those

and meaning that that one is more important just because more people have mentioned it.

I mean, it's interesting and you can get a sense of that just by browsing through the comments, but we didn't want to encourage people to just fill the inbox with more of the same. We wanted it to be really listing individual and, you know, distinct comments that would really be helpful to the committee so we didn't really go in that direction -- although we do have information as the Working Group does want that information we're happy to share it.

DR. HSAIO: Okay, thanks.

DR. HERTZ-PICCIOTTO: Yes, I thought one of the – some of the most interesting comments were in that question that was at the end -- the – about multiple themes or just the bin in which the responses were kind of placed and, you know, they were really quite a number of interesting ones, but in particular, microbiome came up repeatedly and so I thought that's the, you know, I agree with, but also, you know, I think it's interesting that that, you know, that idea has really captured the - some ethics of the public's attention and epigenetics as well -- which you already mentioned, but just wanted to -- and I think the microbiome I think a lot of people are looking to because of the comorbidity's of GI symptoms and the possibility that microbiomes was playing a role in that so I think it should only (unintelligible) that comorbidity issue yes, yes. It's – that was one thing to mention.

DR. DANIELS: Thank you. Other comments on the public comments? You know, you're free to continue…

DR. HALLADAY: Sorry, this is Alycia…

DR. DANIELS: All right, go ahead. Is there somebody…

DR. HALLADAY: (Unintelligible). So the aspirational goal work talks about prevention of, you know, prevention of disabilities and challenges rather than "It". When - I guess I'm thinking when people came in and said, "We shouldn't be preventing Autism," I think that they were not thinking of it as – they were thinking of it that's it's a big "It", right, so they were saying "Okay, can 'It' be prevented," and not necessarily thinking about prevention being prevention of certain challenges or certain behaviors that have mitigated would improve the quality of life of someone.

So, I guess, you know, I guess I would make that comment that I – that when people who are – when people come from that perspective I think that they feel like "It" is the big "It" and not necessarily the aspirational goal as it's been kind of specifically stated. Is that clear?

DR. DANIELS: Yes, and so toward the end of the call I have some time for us to talk about that because if the Working Group feels like this - modify the chapter title, it's something that we can look into.

DR. ETZEL: So this is Ruth and I actually would like us to talk in terms of primary, secondary, and tertiary prevention because I think that would clarify, you know, the whole issue and really make it clear cut that we want to do primary prevention, you know, reducing air pollution if that's a ideological risk factor, but we also need to do secondary and tertiary prevention.

DR. DANIELS: So can you elaborate on that especially for members of the public that might not be familiar with these concepts?

DR. ETZEL: So, sure. The idea of primary prevention would be to actually prevent the

exposures that may be part of the ideologic pathway. Secondary prevention would be screening programs, for example, and tertiary prevention would be working to make sure that the concept disabilities that are experienced are minimized.

DR. DANIELS: Thank you.

DR. AMARAL: Susan, this is David and I guess I just want to follow-up on what I said before and I think, you know, the kinds of things that I hear that parents are most concerned about treating or curing or preventing some of the medical issues like GI disease or seizure disorders or autoimmune disease. so, I, you know, or severe food allergies, so I do think that it's important that, you know, we maybe fractionate the big "It" into (unintelligible) other associated disorders related to Autism and, you know, so, "What are we trying to prevent and treat in terms of the challenges?"

But "challenge" sounds a little too vague to me, but, you know, if we talk about some of these things like GI disease or, you know, seizure disorders, I mean, I think maybe there will be more consensus that those are something that we do want to target.

DR. DANIELS: And I think that that's certainly an area you could write about in the strategic plan. Even, you know, in the beginning of your chapter you can lay that out as kind of a foundation, "What do you mean by prevention and what are your goals in that area?" so I think that's very viable for you all to do.

DR. AMARAL: Okay, okay.

DR. HERTZ-PICCIOTTO: Sorry, David, you cut out for a few minutes at least on my end. We're – would you also include, I mean, you were talking mostly about what we think of this comorbidity as not aspects of the core symptom and while I

appreciate the, I mean, I keep spilling over into this issue -- the neurodiversity issue -- but when we are talking about prevention I think that it - the issue of the, you know, for some people the core symptoms are a series disability and a deficit that they struggle with as a deficit and being able to, you know, carry on their aspects of the life in a society where, you know, interactions are so important to other people so I wouldn't limit it and I don't think you were saying that, but I just, you know, maybe clarify because I would think that core symptoms when they are disabling as opposed to enhancing people's abilities in certain directions as well as the comorbidity would be part of the prevention.

Just one other issue of prevention. I read a few comments on, you know, screening as being prevention. I actually see screening as being just the first step towards the secondary prevention of identifying who is at the high-risk and then the next thing (unintelligible), you know, "What can we do to help those people?" and I'm sure that's what you meant too, so…

DR. AMARAL: Yes. No, no, I would tend to agree with you Irva. I, you know, I do think that there is more discussion about social impairment and whether, you know, how that should be treated or, you know, what is associated with social impairments so, I mean, I think in the neurodiversity agenda, you know, there are individuals who say, "Well, okay, so if my social impairment, you know, can be treated I would rather have it treated or understood because there are all these valuable other attributes that I have to associate it with my Autism," but, and so I think there's much discussions there and I agree with you that it's very debilitating then, you know, that should be a target for treatment as well, but I don't think anybody would disagree or I may be wrong, you know, that serious gastrointestinal problems or serious epilepsy which should be a target for, you know, prevention

and treatment if we can do that and I doubt that there's going to be anything that could be done that's going to be a "magic bullet" that's going to solve all those issues.

So, you know, I, yes, so I do think that there's, you know, there are, you know, there are individuals with Autism who, you know, have the core features, but none of the other disabilities -- comorbid disabilities -- and they probably have a different perspective on prevention than somebody who's a child that's, you know, nonverbal and low IQ and has GI problems and all the other things that we associate with the most serious difficulties of Autism.

DR. NEWSCHAFFER: Hi. This is Craig. I think the other idea that may be helpful as the group grapples with this is thinking about the behavioral impairments. Some of the rethinking that's gone and also some of the empirical research that's gone on particularly from the genetic side of things in terms of thinking about the behavioral impairments of Autism as being continuous traits as opposed to dichotomous categories, right, that gets the Alycia's idea about the "It".

We're not really talking about an "It", we're talking about a continuum of impairment and then the prevention question becomes one of sort of shifting that distribution and it's not really about eliminating a tail of that distribution and I think that when we get to looking at the literature we'll see that, again, I feel led more by some of the work on the genomic cause of side of things. That kind of paradigm is gaining some traction and I think eventually on the environmental determinance side we may find that it's helpful too to think about our outcomes as related to behavioral impairments of Autism as being continuous trait so I think that may help us too in terms of grappling with this very difficult point that's brought up by the community comments

in terms of – and thinking about the outcomes in a little bit of a different way.

DR. DANIELS: Thank you. More comments on that? Seems like that would be an important theme to expand upon in your writing and it's kind of a -an expansion of what the committee had worked on previously. So do we have anything else on public comment that's - we need to talk about before we…

DR. HERTZ-PICCIOTTO: There was one other issue that was raised by a number of people in the public and that was not limiting to the prenatal environment and I think that's really important one. I think for good reason we've been focusing a lot on the prenatal period and I certainly see that as probably being the most critical, but it seems also quite likely that there are, you know, early life postnatal characteristics that also play a role even in or the sense of primary prevention, but also, of course, on the more secondary and tertiary so just to make that a little bit more explicit and, you know, provides some of the rationale behind that from the, you know, the basics -- biology and science -- as it unfolds.

DR. DANIELS: Thank you.

DR. HERTZ-PICCIOTTO: And not to say that we really know, but really that there are reasons. You know, that there are reasons and to at this point not to preclude the postnatal which I've heard people say at the INFAR meetings that it's got to be prenatal -- so I think that it's still - certainly it, you know, it's – at minimum, it should be an open question.

DR. LAWLER: So this is Cindy. I agree with Irva for very good reasons. You know, we shifted towards more toward the developmental origins of diseases not that just that occur and present early in life, but even later in life, but I think we may have gone a little bit too far and there is

sort of an additional work to be done to understand how ongoing exposures can shape the trajectory, you know, over the life span of, you know, any of these phenotypes or, you know, how these impairments express themselves and, you know, how some of them might be resolved so there's, you know, I think it, you know, plays into this idea that when we talk about what causes it that's it's either, you know, "Yes" or "No" and you have to either intervene very early and there's no going back and that I think is, you know, create some of this pushback that we hear from in the community about, you know, "What do you mean," you know, that to be cured or prevent it and it's much more nuance than that and that in kind of addressing the impact of ongoing exposures on some of the challenges and impairments could, I think, you know, dovetail with a better way of thinking about this.

DR. DANIELS: Thank you. Any other questions?

DR. HERTZ-PICCIOTTO: Yes, this…

DR. DANIELS: Go ahead.

DR. HERTZ-PICCIOTTO: Yes, just a very last thing. I want to say I was looking at one here there I think it sums it up so beautifully in terms of why this entire Question 3 matters is that -- and this is in occupational therapy – a person signed as an occupational therapist instead -- said -- sorry, it's little noisy -- "Genetic and environmental risk factors are of priority because those areas may be able to be controlled for preventions of disease. If I knew what genetic makeup caused this disease and I was a carrier I may decide to not have children. In addition, if environmental factors such as pesticides and beauty products that are ingested into the blood stream could be a cause of Autism, I wouldn't buy or use that product."

Okay, just so down to earth and it, you know, it can help people make decisions and so, you know, it's kind of the essence of what this question I think is about.

DR. DANIELS: Thank you. Further comments? All right, well let's move onto the next portion of our discussion today. So we're trying to set up some background that you can use as your developing the chapter you're going to be writing which is going to be on the topic of genetic and environmental risk factors. I provided a list of topics for you taken from previous versions of the strategic plan and some of the discussion that we had on the previous call but try to put together a few bins that you might be able to use in your writing although you're welcome to change it around.

The main thing is that we don't want to have so many bins that it gets confusing. We want to try to group some things together, but we want to be able to go through and talk about some of the important progress that's been made across the entire field. And so in looking at the list of topics here, are there some notable areas of progress that you want to highlight in the strategic plan update that have happened since we left updated the plan? Any major changes in the field, paradigm shift, breakthroughs…?

DR. HERTZ-PICCIOTTO: What year was the last update? I was a little confused.

DR. DANIELS: It was – the last time we did it – published an update was in 2014. It was labeled the "2013 Strategic Plan Update" and we're not being really strict about dates here, but really…

DR. HERTZ-PICCIOTTO: Okay.

DR. DANIELS: …in, you know, fairly recent years have there been some major changes that have influenced our thinking about this field and I

think last time we got into some discussions about, but wanted to give you a chance to name some important advances we should recognize.

DR. HSAIO: This is Elaine Hsaio. I'd like to just highlight advancements in the microbiome area. You know that it did make into your previous update, but I think in recent years it's really advanced quite a bit such that with animal studies there are several more findings that microbiome changes can contribute to social abnormalities and communication deficits.

In some cases -- in known Autism models and I'd also like to highlight on the human side -- there still is much discrepancy about whether there's a true microbiome signature for Autism; although there are several independent findings of microbiome differences in Autism. But I think that general field has advanced such that now there are well-defined cases or microbiome can modulate immune system development, contribute to GI abnormalities and so the big question or conceptual other advances here are whether microbiome changes could serve as an interface between some of the environmental risk factors that we're interested in in genetic susceptibility much like epigenetics in that there are cases now where a short-term environmental insult can modify the microbiome long-term changes in microbiome that are persistent can continue to contribute to immune dysregulation and GI dysfunction. And so I do want to highlight that there's so much to do in this area, but there have been significant advances and a lot of interest in continuing this work.

DR. AMARAL: So Susan, this is David, and Elaine I agree with you. I think that's an important area. And, you know, what would be really helpful in writing this chapter if since you're, you know, involved in this area is if -- and this is extra work -- but if you would be willing to, you know, write a short summary of

where you think this area stands and whether the, you know, most important contributions in terms of the literature in the last few years, you know, a concise sort of statement about where the field stands and what needs to be done would really be helpful to Cindy and I as we, you know, help to try to put this chapter together -- so if you're willing to do that, that would be terrific.

If not, that's fine too, but we'll, you know, we can do it other ways, but given that you're, you know, directly, you know, involved in it would be really helpful to get your insight.

DR. HSAIO: Sure, I'd be glad to provide a short, I guess, concise statements on this and I can also forward you a review. I've written, I guess, a postdoc in my lab has written a review on this exact topic. It's now - just came out in Biological Psychiatry.

DR. AMARAL: Oh, terrific. Yes, that's great.

DR. BERNIER: So I would -- this is Rafe speaking -- I would say that certainly paradigm a manic shift at all, but even in the past three years who made significant advances in our confidence about certain particular risk genes or genetic events that are playing risk factors and I – so I would say that's not a, you know, a change in which we're thinking about it, but the pace is quick and rapid and what that's allowed for whether increased confidence about particular genes is and now we can at least start to think more clearly about genetically defined --so subgroups -- in Autism and that can then, you know, as we sort of look at these are questions further down the list, I suppose, but think about opportunity that would allow us for us to understand better between the relationships between gene environments and interaction open up the idea for functional studies in future treatment targets -- so, I just want to think about most notable areas of progress I actually

sort of think about our increased confidence and the number of genes that we're finding that are associated with Autism.

DR. DANIELS: Great. Thank you.

DR. HALLADAY: Hi. This is Alycia. I just want to add -- and this is probably is a crossover between a couple of the questions -- so I'm not saying that it's a 100%, you know…

DR. DANIELS: Feel free to do that. I just provided the discussion questions to give you an idea of what kind of information that we're looking for, but if it makes more sense for you to talk about multiple questions on the same topic at one time that's totally fine.

DR. HALLADAY: Okay.

DR. DANIELS: We're taking good notes.

DR. HALLADAY: Well, I'll just…

DR. DANIELS: …to help.

DR. HALLADAY: Yes, I'll just add that I think our understanding of females with Autism has really advanced in, you know, and really accelerated in the last few years. I'm not saying it was absent before, but really in the last few years as it accelerated and I put it in Question 3 or I think about it in Question 3 because I think that researchers may have thought about (unintelligible) in male or what why is – why are males pore times to likely to get a diagnosis and there's a lot of different reasons for that which (unintelligible) wouldn't be in this category.

But I think that there is now some thought about what, in fact, maybe protecting girls including whatever genes or located around IQ or something like that -- so I'd put it in Question

3, but I definitely don't think that it's exclusive to Question 3.

DR. LAWLER: So this is Cindy. I think to follow onto that I agree there is this emerging understanding of sort of etiology around male females with Autism, but I think this also provides and I think this provides an opportunity because it begins to marry what we're think more about in terms of endocrine active compounds as exposures and, you know, it's an opportunity and we oftentimes ad environmental health sciences don't have sample sizes large enough where we can look at girls separately, but I - there's probably good, you know good day to now emerging that we should start looking at, you know, sort of sex dependent, effects of exposures -- so again, the progress proves presents an opportunity, I think that, and that opportunity is what really fits under this question in my mind.

DR. DANIELS: Cindy, are there barriers that need to be removed to make to be able to make that happen?

DR. LAWLER: I'll let Irva and Craig talk to that – speak to that as, you know, epidemiologists that try to pull together these kinds of studies and, you know, to kind of challenge us around. Sample size, I guess, is the most obvious one that comes to mind. There's a separate set related to how you define and endocronoctive compound, how you measure them.

Some of them are more ephemeral and very difficult to, you know, get a historical record of but I'll – let me – Craig, do you want to jump in and talk about this? I know you've been interested in (unintelligible) or endocrine disrupting compounds in the context of Autism.

DR. NEWSCHAFFER: Yes, and I would Susan's call for clarification pertain to the EDC chemicals and in parulis whether it was the challenges of

looking at gender specific effects of those exposures or both.

DR. DANIELS: Both.

DR. NEWSCHAFFER: I mean, I think that you know, Susan and Eruv is probably even more qualified than I am I think exposure assessment remains a challenge especially if we're interested in assessing exposure to these (unintelligible) chemicals in patrilocal (unintelligible) windows of interest and while I agree with the past comments that we do need to be thinking about time periods other than the prenatal period I think the prenatal period for a lot of reasons that has also been acknowledged will continue to be a period of interest so if we're talking about biomarkers that exposure the EDC and other exogenous chemicals that requires the assembly of bio-assessments from that period -- which, as you can imagine, is a challenge.

And then if you overlay and in particular the interest of the idea of looking at females subpopulation you know the demographic challenge of the lower event rate even if that male/female ratio is shifting somewhat, you know, again, becomes an increasing stress around sample size, but difficult to obtain bio samples in the ideological windows that we think are of interest and then the additional challenge of being able to look at the female subgroup and whatever cohorts we can put together really stresses this and I think also, yes, so I'll pause there and see if Eruv has anything to add.

DR. HERTZ-PICCIOTTO: Yes, well, Craig kind of hit at the "Achilles heel" of environmental eidolon whitetail is exposure to science and I think that the there's the beginnings of a field and it's really been in the last two years that some work by, you know, toxicologists, chemists, and some more who are really trying to find out,

you know, as environmentalist we also jealous, you know?

Sure it costs money, but you know, one, you know, we with one fell swoop can actually characterize the entire, you know, genome and to find in different ways, of course, and, you know, we're still looking at, you know, one's and two's and maybe classes that might have 200 contents but we're still looking at five or six of them so this idea of an exposed approach and also having a, you know, going from, you know, just as geneticists candidate genes to (unintelligible) trying to figure out how we can start – stop going from stop focusing only on our candidate exposures, but being able to do you know untargeted analysis and so that you know, that work is in development of tools are being developed.

They're not – they're still, you know, in their very, very early stage where maybe genetics were about, you know, you know, 15, 20 years ago in terms of that and hopefully it won't take us as long to at least to get to a more feasible tool in that regards. For the questions of the sex differences, you know, I think it – there should be these "two sides of the coin".

Why is that boys are in a much higher risk and, you know, what is it that we girls in terms of, you know, in lower risk and are there particular things and, you know, I think probably the two are have to be linked in a way and that, you know, boys are a higher risk here and lots of environmental kinds of conditions and it's, you know, it's a bigger mystery than just Autism, but it certainly continues be challenging and I think there is a number of interesting pathways that are being pursued in that regard.

The hormone influences on the brain, I think, are starting to, you know, attract attention. Now I think there's been mostly descriptive work that, you know, (Baron Colon) has championed for years

now and, you know, some of the biology, think, is starting to draw attention – potential role of the fetal adrenal which is actually the largest gland in the fetus and turns out it may communicate quite directly with the placenta. The placenta is different when there's a boy baby than a girl baby.

They actually are – you can know which sex it is by looking at what the placenta does and so I think there's a lot of interesting biology that can be, you know, linked to understanding some of those questions and, yes, I think a number of things that happened in the last few years that are starting to, you know, open up a way that we can interrogate environmental influences and smarter ways.

DR. DANIELS: Do you have any particular examples of ways that we should be considering?

DR. HERTZ-PICCIOTTO: So I think, you know, some of the complexity it relates to, you know, starting with epigenetics and, you know, microbiome, the microbiome today is really just (unintelligible) in it probably was a 100 years ago. Certainly it's very different between developed and underdeveloped countries in huge ways. And so you know, starting to look at how environment influences the microbiome what you know, what it means that you know, (unintelligible), anybody who has been born by a C section doesn't carry and none of their progeny forever, will carry some of the really important, mentioned above, bacteria that play a really important role in early development and protection for the newborn.

Some of the studies on the adrenal suggested it's really critical in getting the right sex steroids to the brain early on in gestation. So, you know, and of course, the endocrine destructing chemicals in our environment, might be interfering

with that. So that is an, I think, promising area. I'm sure others have suggestions.

DR. NEWSCHAFFER: Well I think Susan, that Irva's allusion to EXPOsOMICS I think is important. And I think if we want to be forward thinking we'll probably want to pay attention to, and I think this is what your outline implies, we'll want to pay attention to some of the advances that have gone on from the exposure science field, sort of agnostic to particular outcomes that we might be interested in.

Because some of those techniques are on the verge of being ready to be applied to our autism studies. But the literature that we may have to review at this point, may really be more outcome agnostic. But I think it's important that we highlight that. I also think there are potential approaches relating to EXPOsOMICS that have been characterized as so-called meeting in the middle approaches, where you have some information on exposures of interest that could be endocrine disrupting chemicals.

And an outcome of interest like autism spectrum disorders or behaviors associated with those. And you also build into your study some of these candidate platforms for measuring the exposome, whether it's proteomics or epigenetics or metabolomics. And there are some techniques that have been implied that can be applied where you sort of look for the exposure - you look for the overlay between the signal associated with your outcome and your exposures of interest.

And this has been proposed as a way, potentially to advance the field of higher dimensional assessment of exposure in the context of any one condition, like autism. So it may be that, you know, that might be sort of an approach that we might want to think about highlighting. I don't quite know whether I'm set on that yet. But I do think that looking to EXPOsOMICS, being

cautious, but being forward looking will be important and that will be an interesting section of this report.

DR. DANIELS: Thank you both for elaborating on that. Other comments about progress, opportunities?

DR. NEWSCHAFFER: I just wanted to - I'll be very brief and I'm a little out of place. But just to – Rafe emphasized on the genomics side, the idea that there is some more certainty about a wider range of candidate genes. The other finding that I noticed, is just the pathway findings of coming out of genomics. And you may have assumed that that would be highlighted under that bullet. But I think that's going to be really exciting for the genetically oriented folks on our team, to sort of look at the advances that have been made, coming from genomics and point of care potential common ideologic pathways.

DR. HALLADAY: This is Alycia. I 100% agree with that.

DR. HERTZ-PICCIOTTO: You know, there's another aspect to the environmental research that - and how mechanistics and environmental studies - how do I put this - that we think of genes as being raised to learn about mechanisms, but so are environmental factors. And I think going forward and, you know, this is happening with any challenge, you know, graft on metals and looking at DNA methylation, is one example.

And there are a number of others where ranking the environment not just in the black box epidemiology, you know, what we call black box epidemiology, where you kind of ignore everything in between and you just look at your environment factor and your final outcome. But for the teasing apart of those pieces, whether it's a changing gene expression or working by, you know, immune pathways or hormonal ones or what have you.

And I think that the field is really now starting to do that, where three years ago, five years ago, we could think about it but, you know, the grants that have been started, had not yet really gained enough either participants or, you know, funding or what have you, to really do that kind of science. So I think we're really poised to start making some, you know, I think faster and more - and deeper progress, because of those developments and the way in which, you know, the research projects now are taking on these more complex issues.

Which brings up also the question of mixtures. And, you know, I know NIHS has been trying to promote immune methods developments in that area. And I think there are now some tools out there, some of the work that's come out of Mount Sinai and in that area, more quantile progression and other, you know, I think there are a few other people working on this question a little bit more, way more. Particularly because, you know, well okay, I'll stop there.

Somebody's taking notes, is that right?

DR. DANIELS: Yes. We're taking notes.

DR. HERTZ-PICCIOTTO: Okay.

DR. DANIELS: No other comments?

(No response.)

DR. DANIELS: So what are some of the big opportunities that we want to take advantage of in the next strategic plan that have been set up by previous research. And you've already been commenting on some, but additional ones that anyone wants to share?

DR. HERTZ-PICCIOTTO: So I'm wondering about - I didn't really look at what there is on that, but

I know - I think you mentioned in one of the handouts about animal models. And, you know, more potential I think, to take some of the epidemiology and have the animal model field start interrogating again, some of these deeper things that they may be able to do more quickly in an animal model than they can do in a human setting, just because development is basically quicker.

And, you know, rodents aren't always the best models and the primate model maybe can be utilized somewhat more in this area, given that it has a, you know, a lot of aspects (unintelligible) I think are quite different for the non-human primates in comparison to humans, but there's a greater similarity. That might be another area where there could be opportunities.

DR. DANIELS: Thank you. Others?

DR. LAWLER: This is Cindy. And I would like somebody on the call that has genetics expertise, to maybe talk a little bit about the issue of how common variation could be approached, because I think that's potentially a real obstacle. Because it's an - environmental exposures are interacting with common variation. And the common variation is, you know, combinations of many, many different genes. How do you even begin to approach that?

But if that like carries a lot of the risk than, you know, we need to think through it. You know, there are some population based mouse resources that I don't think have been applied in the context of autism. But, you know, in the context of other sort of complex phenotypes that really, you know, could potentially be useful. But I wanted to maybe hear from the genetics folks about the current thinking around the role of common variation and how to even approach that.

DR. BERNIER: So this is Rafe. If I can jump in a little bit and just to say that I would definitely defer to the other folks on the

workgroup here to talk more about common variation. But I think part of the reason for focusing on rare variance to begin with, is it's a lower hanging fruit. Because as you say, it's very complicated to think about how common variation would interact with so many different variables and all the different variables out of the potential variants that are out there.

You know, we can get a lot more bang for our buck right now, in terms of informing and making sense of findings, by focusing on the rare variants. You know, we started with the no variants because of the lowest of the low hanging fruit. And now we've been moving our way through inherited and (missing) variants which are again, higher up on the ladder of the fruit tree so to speak. And so - and we've still got a lot of work to go there.

So I guess my - so my perspective, I think folks so far has yielded quite a lot in a very short amount of time. And we're still not finished with that. And so anyway, I guess I'd stop there and say we should probably hear from the molecular folks to figure out how we would deal with that in terms of common variation. But I think we've done a lot of great work with jus focusing on rare variants.

And we still have more to work - more work to do there especially as folks are moving towards thinking about whole genome sequencing and really moving into that fear. So far we've been focusing on, you know, exome targeted and chromosome micro-array and that's great. But we've still got another whole big versioning approach with whole genome sequencing focusing on those sort of rare variants. I'm using air quotes there.

DR. AMARAL: So this is David. And I just want to agree with Rafe that actually one of the genes that he was involved in highlighting the CHDA gene, is now not only being looked at in humans,

but in both mouse models and there are monkey models being developed in Japan and China. And, you know, I think in terms of low hanging fruit, as he says, and an opportunity, if at least we were to understand what neurobiological alterations are induced by mutations in that gene, in either the mouse with the monkey model leading to impairments and the behaviors characteristic of autism, that would be a huge advance.

And, you know, may just provide prototypes for our understanding of what leads to autism. And so - and unfortunately, I think our genetic folks are absent from, you know, beyond (Rafe), are absent from this call. So I think it's a good question Cindy and one that, you know, we should, you know, pose when they get back on the line. But I do think in terms of, you know, proximal kinds of progress, focusing on these highly penetrant mutations that are coming from the human literature, is at least, in my naïve sense, the way to go.

And I'd agree with Rafe that this is something that we should highlight in the document.

DR. NEWSCHAFFER: Yes. This is Craig and I'm - far be it - I'm not trying to fill the spaces of our genetics colleagues. I'm certainly not qualified to do that. But to Cindy's point of the potential importance of common variants in environment interaction mechanisms, I do think we probably need to keep on the table for discussion in this year's report, sort of a challenge of trying to find ways to incorporate environmental exposure measures into large genomic data sets.

Because now - and Rafe can correct me, but one of the secrets to sort of, you know, discovering through common variants, because of the weakness of their main effect signal is just, you know, bigger size of cohorts. But, you know, if those common variants are interacting with certain environmental exposures, when you look at those

who have this susceptibility gene and the exposure, the idea is that the risk effect will be much larger and easier to detect.

But you need to be able to identify that small group that has both the genotype and the exposure. So, you know, I think there has been some work in this area in terms of identifying measures that sort of light burden collection of certain environmental exposures that could be incorporated into genetic collections. I think certainly, the EXPOsOMICS theme resonates here. If there are ways that we can measure a wide range of exposures or signals of exposure and the same kinds of bio-samples that we collect when we form these large genomic study repositories that would be certainly be great.

Statistical approaches and Danny Fallon would be a good person to comment on this. To do genome-wide interaction studies are coming along. So I think that that's another area that we're going to want to pay attention to, related to common variants.

DR. BERNIER: Yes, Craig. I totally - this is Rafe again. I totally agree with you that the notion of being able to capitalize on sort of, you know, air quotes here, light phenotyping of what's exposures and incorporating that into these large collections, makes so much sense. I think of, you know, the value with the (unintelligible) collection in that it being, you know, folks working together to really collect a good, well characterized sample at the phenotypic level, is very important and really so helpful in terms of advancing our knowledge in the genetics side.

And, you know, I sort of lament that the exposure side is, you know, it wasn't part of the study and that's totally fine. But as we move forward, I think incorporating that into these types of very meaningful collaborations is really important. So I just want to underscore that.

MS. SCOTT: This is Joan. Could we at least come up with, if we were going to have sort of a core set of what those environmental exposures would be, to get some uniformity around what people could collect?

DR. HERTZ-PICCIOTTO: Could you repeat that? I'm sorry. I didn't quite catch what you (unintelligible).

DR. NEWSCHAFFER: I think - I mean I think Alycia or Cindy, I mean there is - there are some initiatives to do that or Irva, you guys probably know a little bit more about them than I do. A core set of environmental exposures.

DR. HALLADAY: So this is Alycia.

DR. HERTZ-PICCIOTTO: Go ahead.

DR. HALLADAY: So I would say that, you know, that if we thought there was a core set then we're wrong, because as we, you know, expand what we know about autism and expand even our genetic knowledge, so you touched on Craig, the idea of looking at genomic networks. And then Irva pointed out that it's not just genetic networks, it's the way that the environment acts on those genetic networks or vice versa. So, you know, I hate - personally, I think that there may be some like really key exposures that may touch on things that we know about, right?

So like things that perturb the immune system during development. I mean I think things like experimental models like - and (Elaine) would know more about like lipopolysaccharide or immune disturbance as being one, you know, easy target. But I think that in terms of the tens of thousands of chemicals that we don't know about, I would hate to prioritize - I would hate to say one is the standard over another, other than the ones that we're pretty sure about like, you know,

prenatal valproic acid or immune - things that challenge the immune system during pregnancy.

But, you know, I would hate to put in this document, anything that limited the focus of environmental exposures, other than to, you know, perhaps prioritize them, maybe just not limit them. Does that make sense?

DR. HERTZ-PICCIOTTO: I don't even know if I would prioritize - I mean, because we know so little it's - I think there are going to be surprises. I mean we're going for low hanging and mid hanging fruit. And maybe, you know, hopefully we'll pick up some of those low hanging - I mean it's just not obvious where you would go, because what we've learned is it's not just neurotoxins. It's what, you know, everybody's been saying, which is there are all of these pathways that it might be somehow related to neuro inflammation and the immune.

It might be metabolism and, you know, why is it we now have four huge studies now, showing maternal diabetes? You know, what's going on with that? Where, you know, and are there environmental obesogens contributing to the increase in obesity that itself, is perhaps, you know, part of the autism increases? And then of course, you know, the sex ratio does suggest some sort of involvement of (unintelligible). So (unintelligible) operating to so many different pathways.

DR. NEWSCHAFFER: Yes.

DR. HERTZ-PICCIOTTO: And it's just - I just think - I don't think we want to - I second what Alycia said.

DR. NEWSCHAFFER: Yes, so I think I - and Susan, I don't know if you want to spend too much time. I think I reshaped the question in an appropriate way. What I think the comment was, was

- I think the comment came off as the exchange that Rafe and I had about wouldn't it be nice if there were some - and again, I'll use Rafe's air quotes over here in Philadelphia, you know, light exposure collection that could be done appended to genomics work.

And so it wasn't about what is the leading environmental exposures. It was what are the things that we might be able to measure easily that could be explored in concert with genetic risk factors. And I know that there have been some initiatives to try to develop to look at different self-report exposures that are thought to come with some accuracy and that there could be a set - and again, I'm not involved in this initiative but I know it's out of UC Davis. And I think that's how me and Alycia know about it.

So that's where I was trying to point you guys towards. I just - I think I sent it in the wrong direction.

DR. HALLADAY: I think - and no, I'm sorry Craig, that just flew right over me. But I do think to Joan's point, that there could and should and possibly could be better opportunities for, you know, geneticists to, you know, to collect information on environmental factors. And that could be either through self-report or through an aliquot of blood or, you know, some other, you know, I think researchers have thought about this. And if we made that a priority and a strategic plan, we could at least encourage, you know, certain projects to collect environmental data and environmental projects, to make sure that they're collecting genetic data.

And, you know, really, really, really encourage biostatisticians and those that, you know, have expertise in developing models to integrate the two data sets. You know, I think that that would be another - that's something that's had movement, but I agree with Joan, I

didn't - Craig actually clarified the question. So I guess I didn't understand what Joan was thinking before. But yes, I think without getting too specific about what the chemical is, there are ways to standardize methods of assessment.

DR. DANIELS: Thank you for discussion on that. Some other topics that have come up on the call so far, that you might want to elaborate on, are protective factors. Where are we with protective factors and what else do we want to know? What are the opportunities there?

DR. AMARAL: Yes, Susan. I raised that question earlier about folic acid. And I think it's an important one. I'm not an expert on that, so I don't really have any definitive information. But I know that I used to be able to say to lay audiences that the one thing that you can do to reduce the likelihood of autism, is to, based on work that was initially done by Irva and Rebecca Schmidt here is, you know, to begin prenatal vitamins earlier than after the pregnancy is determined.

And now I wonder whether that's, you know, that has been called into question or not. But - and there may be other topics like that. But it seems to me that this chapter should also have a section on what is known about current preventive measures and what is the certainty that can be ascribed to those - something like folic acid? So again, I'd love to hear, you know, some conversation about that.

DR. LAWLER: So this is Cindy. Two things come to mind. I agree the folic acid story is probably a very nuanced one and we're not quite sure what that - those response looks like, not just for autism but other endpoints as well. I know there has been a lot of interest in understanding that. And then the second thing that comes to mind David, when you were talking about that, is this

idea of how do we make sure that we're crafting the right messages…

DR. AMARAL: Right.

DR. LAWLER: …for the, you know, for the public. Or, you know, what actions and, you know, we don't want to be in a - we don't want it to be the case that we're just kind of adding to the confusion. You know, a year ago they said yes, definitely take folic acid. And, you know, if a little bit is good, shouldn't I take more? Well no. But that's - then that becomes, you know, its own kind of challenge. And nobody trusts anything. So I - we may want to give some thought to how we kind of translate any of our findings into public health messages…

DR. AMARAL: Yes. I agree with you Cindy.

DR. LAWLER: …to be really careful that we don't, you know, make mistakes that end up doing more harm than good.

DR. AMARAL: I agree with you Cindy. And maybe, you know, once we get more comment on this, this could be sort of an exemplar of a situation where, you know, there has been various messages coming out and, you know, how we need to deal with these kinds of topics in the future. Because I, you know, I do think it's important to send a clear message as much as possible, based on research findings to the community.

DR. LAWLER: Yes. I mean I think, you know, that paper - we'll have to see when it goes through peer review. And there were some issues as to who those people were who were taking the very high level that they may be taken for medical reasons. So…

DR. AMARAL: Right.

DR. HERTZ-PICCIOTTO: …you know, I'm not sure - we don't really know yet at this point what that finding will be - will turn out to look like. But in terms of a larger question, I think it's - no, I'm really glad you're raising that David. And I would love to see this report talk about that. You know, what some of the other findings that are turning out seemingly to be quite robust, for instance, is this diabetes finding. And so that's, you know, people controlling their blood sugar.

You know, that story is, you know, again, it's mostly large studies without necessarily understanding the mechanism. But there was another analysis of 12 small studies that came out with the very clear answer. And then (unintelligible) cities looking at some, you know, medical records and with, you know, some of the cities have hundreds of thousands of people with some very strong relationships there.

So - and of course, you know, there's - diabetes is something that should be prevented for (unintelligible) along too.

Dr. Amaral: Yes. Are those papers that have come out this year?

DR. HERTZ-PICCIOTTO: Fifteen and '16. I mentioned - 2015 and 2016, the four big papers. It'll be - when I get you my paper from the keynote, it was a table I showed during that talk.

Dr. Amaral: Okay.

DR. HERTZ-PICCIOTTO: So, you know, maybe that should go in this report as well.

DR. AMARAL: Well I'm thinking that that should go into the IACC, you know…

((Crosstalk))

DR. HERTZ-PICCIOTTO: …go in this report too.

Dr. Amaral: Okay.

DR. HERTZ-PICCIOTTO: So, you know, that's one. And then there may be others where there are some, you know, not yet firm yes, we can say this is definitely going to make - be helpful. But there are a lot of environmental chemicals that aren't, you know, serving necessarily a positive, you know, there's not a huge benefit necessarily, to having (valley) in our environment and I don't know, mount the evidence, you know, for some of these environmental chemicals that, you know, if you can, you know, that there are ways you might be able to avoid them or reduce your exposures.

And the, you know, I guess one of the problems is, you know, when the research, you know, isn't fully all there what is the - how do you craft an appropriate public health message?

DR. AMARAL: Well I think that that's okay. I mean if there's, you know, sufficient research to suggest that, you know, controlling blood levels like glucose levels in diabetes, is an important process to decrease risk of having a child with autism. You know, certainly it can be moderated in terms of how strong the statement is made. But I think it's important to, you know, make those kinds of statements and just document, because we're talking about all of these risks but we don't really say anything about, you know, what can be done.

And, you know, I think the other important thing too, is that the statements have to be crafted so that they're not putting blame on people. I mean but, you know, to my mind, you know, if you - if the evidence is suggesting that well controlled diabetes is going to decrease risk, I mean that's really an important statement to put out there. And then certainly the individuals can make a choice on what they're going to do.

But at least, you know, the knowledge that's coming from research is being presented and that's an important contribution.

DR. NEWSCHAFFER: I think the other thing that we can maybe do in this area, is to suggest that we start thinking in terms of population attributable risks. And when you start thinking about, you know, taking action you want to be thinking about the population attributable risk and not just the relative risk. And, you know, which is a function of how common an exposure is and how strong an effect is, or how common, you know, what kind of change do you think you can see in the proportion of individuals who are taking a protective factor and then what's the attendant risk decrease that you can see?

So it's just another way that we can sort of look at our emerging evidence base with more of an eye towards action and prevention. Or maybe we should be thinking about or asking researchers to start doing that a little bit more often than they do right now.

DR. DANIELS: Any other discussion on that? With regard to communication about genetic risk, have we made any progress there? Are there other messages that need to be provided in that arena?

DR. AMARAL: So…

DR. DANIELS: I know, we don't have all our genetic risk people on the line, but…

DR. AMARAL: I think we need to have (Steve Scherr) on the line. Because I know that they at Sick Kids in Toronto, have been putting a lot of effort into, you know, they have a large whole genome sequencing study going on. And I, you know, I know that it's a very difficult topic. And, you know, probably one that, you know, it would be great to get his input on where their thinking is

at the moment. But it's not a topic that, you know, can be handled easily.

So it might be worthwhile Susan, just to wait until we have Evan and Steve on the line, to get into that.

DR. DANIELS: Right. And we can definitely do that offline if you're starting to do your writing. You can ask them to help out with this, you know, the framing of that discussion.

DR. AMARAL: Right.

DR. DANIELS: So on a couple of…

DR. ETZEL: Can I just ask a clarifying question about that question? Is the question about communicating risks associated with various exposures? Is that the risk that we're talking about communicating?

DR. AMARAL: No. I thought the question was genetic risk. So if you have a mutation that's been associated with autism, how do you communicate that to the family? And what are the predictions based on that? And the problem is that most of the autism associated genes as I understand it are, you know, so - that lack penetrants. And so the prediction is - of outcome is difficult and, you know, there are also other genes that may be associated with comorbid symptoms like epilepsy that, you know, are not going to be associated specifically with autism.

So I think, you know, there is a struggle with people who are getting more and more detailed genetic data on individuals that, you know, that it's hard for them to come up with a straightforward way of communicating the risk to the family. And, you know, what the implications for lifespan.

((Crosstalk))

DR. ETZEL: From a point of clarification, these are individuals that already have autism in the family and that are being sequenced because of that and genes are being found. Are we talking about in normal populations who are undergoing sequencing for - or for some other indication, and genetic variants associated with autism is identified? Which group are we talking about here, because - and there's a lot going on in this area that's not necessarily specific, you know, to autism, but in other - and genetic variations associated with a whole variety of things.

DR. AMARAL: Right. Yes, well I - again, I think, you know, it'd be best to have (Steve) and (Evan) here to get into this because again, they are the ones who are dealing with this on sort of a daily basis. So I don't want to misspeak, unless (Rafe) you want to contribute something. But, you know, I know just listening in on conversations that their group has, it is a, you know, sort of very conflicted, difficult topic to try and work through.

DR. BERNIER: Yes. Oh, I totally agree. I think it would be great to have them onboard and that makes sense to me. Wait for them. Yes.

DR. DANIELS: Great. That sounds good. This is Susan. So I had a couple of question here about the workforce. So with the research workforce, are there any particular needs that you see for developing certain portions of the workforce, for particular cross disciplinary training or anything like that? So do we have a fairly adequate workforce to address these questions of genetic and environmental risk factors?

DR. HALLADAY: This is Alycia. I would say we don't. I'm not saying that we have an adequate, you know, workforce to address any of the questions. But I think since the questions are starting to emerge, some of the - what we - what I

feel like we need is new analytics strategies. And early career investigators who are really pushed to think about multidisciplinary approaches and even bring in outside expertise. And I think that's probably going to be consistent across the different (question)s. But I kind of want to make a push for it in this question, that we, you know, need to make sure that there is adequate training in newer kind of analytic techniques.

And, you know, not just, you know, kind of statistical techniques but techniques having to do with, you know, new analysis - new ways to identify DNA, new ways to analyze it, new ways to incorporate the exposome.

((Crosstalk))

DR. NEWSCHAFFER: I think training of researchers with a particular interest in gene environment interaction is important to underscore, because you need to know something about genomics, you need to know something about environmental exposure assessment. You need to know something about novel emerging statistical methods and the extra challenges posed by the, you know, the larger sample size and dimensionality that goes with (unintelligible) data. So I think that's a particularly important area to emphasize training in.

DR. LAWLER: This is Cindy. I would agree wholeheartedly. And we have only a very small pool of trainees and early career investigators that, you know, have that toolkit, that are able to approach this gene environment question for autism. So I would…

DR. HERTZ-PICCIOTTO: Yes. I don't know if we were - oh, I'm sorry.

DR. DANIELS: Go ahead.

DR. HERTZ-PICCIOTTO: Were you done Cindy?

DR. LAWLER: Yes. I'm done.

DR. HERTZ-PICCIOTTO: Okay. Yes. I don't know if we can, you know, how specific we can be and this is I think actual certified training funds, you know, are more, you know, I don't know - of the existing training programs if there are, you know, to what extent one can, you know, the agency (unintelligible) to specify this is particular area of need. But I think this is one that's, you know, there's just - the field still really works so (separately) that it, you know, it's really helpful if the funding agency is putting incentives behind people moving into these cross disciplinary kinds of activities. So if that's something we can put in, that would be great.

DR. DANIELS: Yes. You all can make recommendations around the workforce. We wanted to make sure that every chapter will have some emphasis on that, both in terms of the research workforce and the services workforce. Other thoughts?

MS. SCOTT: I actually think it's really important to also make better connections between the clinicians, the pediatric neurologist and others, who are doing the face to face encounters. And the researchers, by getting the clinicians who are training in neurology and development of disabilities, to understand epidemiology better so that they can do the risk communication. So if we can make sure that that piece is also in there, that would be very helpful.

DR. DANIELS: Anything else in terms of training for research? And then in terms of people who are out in the clinic and in the field, any particular workforce needs that you can see? You just named one. So great, so I think that we've covered that. I think you've had a very robust discussion of some of the needs in the field.

Anything else before we move on, in terms of major priority areas, etc.?

DR. NEWSCHAFFER: Susan, I just had a thought. I think we - you posed before, I think - my memory fades, like you asked about specific opportunities that we saw…

DR. DANIELS: Yes.

DR. NEWSCHAFFER: …emerging. Can I put something else out there?

Dr. Daniels: Yes.

DR. NEWSCHAFFER: I don't know if it's - I think we probably should think about the ECHO initiatives, specifically.

DR. DANIELS: And can you elaborate on that a little in terms of what you're thinking.

DR. NEWSCHAFFER: Well, so the ECHO initiative, as many on the call know, is the environmental Child Health Outcomes initiative funded through the IH Office of the Director, the idea of putting together a synthetic cohort, you know, so the cohort of cohorts, existing children who are already understudied from a variety of different investigations, put together more than 50,000 of these.

And there are going to be some ECHO projects we know that - ECHO cohorts that do have a special interest in autism. But there's also going to be a process which is going to begin very shortly, about trying to figure out - trying to determine what our priority outcomes and potentially exposures and risk factors that this whole group can undertake. And, you know, from the autism field I think that, you know, I feel like it would be important to try to leverage that as much as we possibly can.

And, you know, whether or not - I'm not 100% sure whether that's something that this report or the IACC is thinking about but, you know, somebody should be.

DR. DANIELS: Cindy, do you have any further information about that?

DR. LAWLER: So I know it's - neuro is one of the foci. I think they are not - or they're trying to avoid focusing on any one particular disorder and be more general regarding different facets of children's health. But that, I believe, presents an opportunity to go back to one of the things Craig said earlier in this call, is we can perhaps make progress in autism, by not thinking so much in terms of the dichotomy, you know, cases versus non-cases, but as more continuous traits in the general population.

And those kinds of approaches are ones that might lend themselves to the synthetic cohort where, you know, you're not going to end up accumulating enough, you know, cases that would meet strict criteria of autism, but you could be looking at dimensions of autism, in a large population that could, you know, provide some insight into risk. So that, you know, may be a strategy to think about.

DR. HERTZ-PICCIOTTO: Cindy, do you know how large, now that the awards have been made, actually how large the (end) is for the ones that have been funded, combined?

DR. LAWLER: I do not. I know there's big differences in size, so there are some that are really big. But I'm not directly involved in ECHO at all, so I don't want to, you know, mislead or misspeak at all, about that. I do think it's a good opportunity. And the other opportunity again, not specific to autism but this children's health exposure analysis resource that we launched that is, you know, we'll be soliciting applications for

existing studies that have bio specimens available and that will provide free analyses, both in metabolomics arena to speak more to the exposomic signatures, as well as more targeted analyses.

So that - again, it's open to children's health researchers broadly but, you know, for the autism community, it is an opportunity for us to make sure we take advantage of that existing resource, you know, the same way and make sure that, you know, that we're using that ECHO cohort to the, you know, to the best extent that we can, to advance autism research.

DR. HERTZ-PICCIOTTO: Yes. I mean it might - I think the - yes, that resource - it would be great to have more autism researchers looking into that as a way - and it could help some of those - perhaps some of those genetic studies begin to collect some of the environmental data. That would be useful. And then the other side is I don't know how close we got to 50,000 that were funded. But if they got anywhere near there that might well, in addition to being able to look at that continuum, you know, the continuous scale of autistic trace through the various instruments they have there for that.

But there might well be enough and combined with the one that (unintelligible) one that (trade) put together and are charge - recharge study that might actually be the (induction) in the general cohort to look at, you know, separately from these two autism focused ones, and look at some replication kinds of possibilities. So I guess Craig and I will learn about that in a couple of weeks at our first (ECHO) meeting.

When is our report due for the IACC?

DR. DANIELS: So we're working toward a timeline of trying to get most of our writing done by December. And in January we will be having an IACC meeting. We'd like to take forward at least a

strong draft of your chapter, for the IACC to look at in January. And our ambitious goal is to try to publish this by April for autism awareness month. But, you know, we'll see how everybody does.

I know that everybody has busy schedules and we want you to have enough time to put your information together in the best way possible. So we'll try to facilitate that as much as we can. Are there any other opportunities out there in terms of existing infrastructure that's already been built, that could be expanded upon? I thought we might want to address that in the plan if there is something that you see as a place where we could capitalize on efforts that are already underway.

DR. HERTZ-PICCIOTTO: Okay. Are we going…

DR. HALLADAY: Well this is Alycia, so I could think of other examples but I think that there are a lot of genetic studies to which there's a lot of information. I mean I think one of the - (Rafe) is on the call, but one of the most utilized genetic cohorts in terms of looking specifically at gene environment interactions has been the (Simon Simplex) collection. And, you know, certainly charge is up there but really taking advantage not only of studies that have already looked at gene environment, right, so have collected certain data sets.

But reaching out to those, you know, environmental studies that would be an add on, I think that's similar to what Craig and Irva were talking about with ECHO. But insuring that there is manageable ways to include both genetic and environmental data sets in cohorts where there is one or the other. And certainly there is a number of those opportunities within certain genetic samples and even in environmental samples where, you know, sequencing can be done, whole genome sequencing can be done with those samples. So anyway, that's my plug.

DR. DANIELS: Anything else that we haven't discussed already that we need to add to that? Then I'm going to move to just a brief discussion of the aspirational goal in the title. So we talked about this a little bit earlier in the call, that there is a goal that the committee set for this chapter. And it reads currently, the causes of ASD will be discovered that in form prognosis and treatments and lead to prevention or preemption of the challenges and disabilities of ASD.

And we wanted to get your thoughts on whether you think that's still the overarching goal that eh committee wants to be working towards in supporting research in this area, or are there ways that we would want to modify that? And we don't have to answer it all right here on the phone, but I want to have you thinking about it.

DR. AMARAL: Susan, this is David. I think it sounds fine. The only thing I'm surprised is it doesn't have diagnosis in it. So I would recommend that we add the word diagnosis after informed, so informed diagnosis…

DR. DANIELS: Okay.

DR. AMARAL: …prognosis and treatments. Otherwise, you know, why are we doing all of this?

DR. DANIELS: Sure. Any other immediate thoughts about that? And then on the title, what caused this to happen and can it be prevented? Do we think that that title needs to be adjusted in any way, to reflect the current state of the science?

DR. AMARAL: Even given the discussions that we've had before, I think the title is still fine. You know, the underlying sort of subtitle is should it be prevented? But, you know, we're not saying that. We're just saying what are the causal

factors and, you know, could they be prevented if you wanted to prevent them? So I think that this is fine as is.

DR. DANIELS: Any other thoughts about that? And of course, as you're writing, you'll have a chance to continue to grapple with that, if there are any other issues that come up. So we'll take note of the suggested change. So the next task that's going to be before you all is for me to work with the Chairs on helping you get an outline together. And the Chairs will be getting in touch with various members of the working group and even if we don't have the expertise we need on the working group, other outside individuals to help us with drafting parts of this chapter that will really reflect what the state of the science is in these areas, what are the major needs and opportunities.

And, you know, future goals that we should be working towards. And this will lay a nice foundation for the next conference call where we're going to be talking about the actual objectives that we want to set in the strategic plan. And in previous discussions, with the committee, we talked about reducing the number of objectives. So right now the current strategic plan has 78 objectives which is a pretty large and unwieldy number. And so the committee agreed that we should shoot for about three major - three broad objectives for each of these chapters.

And that would come to a total of 21 that's going to be much more manageable. And each one of them would be a broad statement about an area of the field that you want to push forward. And then we would provide examples of the kinds of projects that would contribute. And then in future years our office would be tracking projects that relate to that overarching goal. And so you'll want to be thinking in future weeks, about if you could pick three areas that you really wanted to focus on to push forward, what would those be?

And if you come up with ideas for actual wording of an objective or even a topic which you'd like to consider an objective, please feel free to email them to me. We'll try to collect them. And I'll also, in an email, solicit that from you later after you've had time to think about it. And we will be having our next call after the IACC meeting that happens on October 26th. So any feedback we have from the committee itself on that date, that would apply to your working group, we'll try to share that with you, so that you have their input and can work on the objectives.

So I don't think that we have the third conference call scheduled yet for your group. But as soon as it is, we will be sending that information out and putting it up on our Web site. So are there any final questions or comments before we wrap up? Well we really appreciate the thoughtful discussion everyone's had about these topics.

I think that you've come up with a number of really promising areas that you can develop in your chapter and that will lay a good foundation for the work of developing the new objectives for the strategic plan. So thanks everyone for being here, and we look forward to talking to you again soon.

DR. AMARAL: Thank you, Susan.

DR. LAWLER: Thank you.

DR. DANIELS: Thanks everyone.

GROUP: Thank you and bye.

(Whereupon, the conference call was adjourned.)