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INTERAGENCY AUTISM COORDINATING COMMITTEE

STRATEGIC PLAN UPDATE

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

Conference Call 2

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PROCEEDINGS:

DR. SUSAN DANIELS: Thank you. Hi, this is Susan Daniels at the Office of Autism Research Coordination at the National Institute of Mental Health where we manage the Interagency Autism Coordinating Committee or the IACC. Welcome to our public audience, to our working group members and our working group chairs to this conference call number 2 of the IACC strategic plan update working group for question 2 on the topic of "How can I understand what's happening?" which is about the underlying biology of autism spectrum disorder.

So just to get started, I'd like to do a brief roll call just to make sure that everyone knows who's on the phone so to start off one of our chairs, Walter Koroshetz.

DR. WALTER KOROSHETZ: Hello everyone, yes Walter here.

DR. DANIELS: Thanks Walter. Louis Reichardt, another one of our co-chairs.

DR. LOUIS REICHARDT: Yes, here.

DR. DANIELS: Thank you. David Amaral? Jim Battey?

DR. JAMES BATTEY: I'm here.

DR. DANIELS: Thanks Jim. Kevin Pelphrey?

DR. KEVIN PELPHREY: I'm here.

DR. DANIELS: Thanks. Rob Ring?

DR. ROBERT RING: Here.

DR. DANIELS: Thank you. Nicole Williams is not going to be able to join us today and Kasha Chawarska is also not going to be able to join us today. Gray Davis?

DR. GRAEME DAVIS: Here.

DR. DANIELS: Thanks, Gray. Heather Hazlett and Shafali Jeste are not going to be on the call today. Eric Klann is going to be calling in a little bit later and Jaime McPartland is going to be calling in a little bit later. Christine Nordahl?

DR. CHRISTINE NORDAHL: I'm here.

DR. DANIELS: Thank you. Elizabeth Redcay?

DR. ELIZABETH REDCAY: Yes, I'm here.

DR. DANIELS: Flora Vaccarino is not going to be able to calling in today. So thank you all for joining us for the second conference call. I don't believe we have any loose ends from the last conference call where we talked about information that was gathered by my office on grants and projects that were funded in 2013 and we had you all look at the portfolio of funded research to make comments on the state of the portfolio and some observations about trends.

We recorded all of that information from the last call and today we're going to be talking about information about progress that's been made in the field. We're going to be discussing information that will go into the section of the strategic plan update that you all will be writing about progress that's been made in the field on research and as well as any kinds of policy updates that affect research.

So to start the conversation today I'd like to turn your attention to a document that I sent out that lists some themes that our office captured from a request for public comment that the IACC put out over the summer to the public. So this request for public comment asked the public to provide us with their concerns, interests, ideas

about the seven areas of the strategic plan as they are now and we collected this information and was able to divide it up according to the strategic plan chapters. We've collected the information that relates to question 2 about the underlying biology of ASD and I did provide you with the full text although you may not have had time to really read all of that at this time and we can always discuss this more in depth on the next call if needed and also the IACC will be discussing the public comments in their upcoming meeting on October 26.

On this list of themes, the themes that we found running through the different public comments included interest in autism genetics and understanding more about the genetics of autism, developmental biology, interest in genetic syndromes and better understanding of how they relate to ASD, work on biomarkers and symptomology, interest in the area of immune and metabolic pathways, cognitive and behavior biology, sex and gender differences, general basic neuroscience, co-occurring conditions with ASD, the molecular biology or the molecular underpinning of ASD, sensory motor end function, the need for more translation on interdisciplinary research, the need to understand – better understand and differentiate subgroups of people with autism, gut and brain interactions.

Some comments that suggested that the current priority areas of strategic plan focuses on appropriate and some comments about certain people that didn't feel that understanding the biology of ASD is a priority so do any of you have comments about these themes and what was in the public comment or any reflections on – as a concern the public has?

DR. KOROSHETZ: I think that there – I didn't see any – this is Walter. I didn't see any big surprises so I think these are the topics that

have come up in the past and I don't think they certainly haven't changed over time.

DR. DANIELS: Thanks. And having done some of these types of requests for public comments in the past, it is true that a lot of the information was the same. There was an increased number on comments on sex and gender differences of that area has been growing but many of the other topics were in public comments before, other comments from the group?

DR. KOROSHETZ: The sex and gender came up – I remember that came up in our last rendition as well. I think that was new when we did the last strategic plan but that was prominent as well.

DR. GUOPING FENG: This is Guoping Feng. I have a comment about the genetic testing. I think we need it. We need to inform the public and most of the genetic testing we cannot pin point yet so just to accept and make it accessible may not do good, actually do harm to the patient and to the population that (unintelligible) without any. So how do we educate the public about the genetic testing of autism is really important.

DR. DANIELS: Thanks.

DR. REDCAY: Actually related to that I noted a few comments of people saying they wanted better dissemination of research and so I think that's also part of that, of not just what topic should they want but maybe some of these things are present and we're not doing a good job translating that and disseminating that research.

DR. PELPHREY: This is Kevin. The second comment – both of those comments really - but also helping the public to understand why we want to do genetic testing and then what it might be good for in terms of personalized approaches to healthcare versus what I think it will never be particularly good for which is actually characterizing risk and

helping the public understand the difference between those two approaches.

DR. DANIELS: Thank you.

DR. KOROSHETZ: Just to clear up Sue I would guess that most of the genetic issues are going to come under question 1, right?

DR. DANIELS: So under question 3 will be risk factors but some of the issues you're talking about where we want to clarify the use of genetic testing, you might be able to – it could go in either chapter 3 or this one or maybe something this group might want to work on that you can give to the chapter 3 folks to put in theirs. But you're talking about use –

DR. KOROSHETZ: On our end the genetics are primarily the clue to help us understand what's underlying biology so as opposed to genetics as a topic in of itself. That'd go with some of the other questions.

DR. DANIELS: Right. I think that you could definitely put something in about this. You could write that up into your –

DR. REICHARDT: Can I just say I think this part as I understand it shouldn't be genetics. It should be impact of genetics on biology and brain function.

DR. KOROSHETZ: Yes I agree. That's true.

DR. DANIELS: Any other comments? Sorry I couldn't hear you.

DR. KOROSHETZ: I was just saying go ahead, yes, Sue.

DR. DANIELS: Okay. So it sounds like you made a few comments on that area so we can move on to the next section here. We'd like to talk about

research progress and the write up that you're going to be doing is largely going to be focused on this. I put together a few discussion questions and want to open the floor to everyone to make comments from your areas of expertise on this. But what do you feel has been some of the most notable areas of recent progress within this whole field of understanding the underlying biology of ASD?

DR. REICHARDT: I would comment I think the development of mouse/rat non-human primate models of risk factors has been essential as well as fish, IPS cells, again for understanding what's all the in particular genetic high risk genetic impact models of autism.

DR. FENG: I want to make sure I understand the question. You want us to comment on the progress made on the program? I just want to understand.

DR. DANIELS: Right now I'm asking you about what recent development has been really groundbreaking, that have changed the field in the last couple years as a setting the stage for what's happened before we get into what we want to do in the future.

DR. FENG: Okay.

DR. DANIELS: So things that you think are really notable that you probably are going to want to include in your chapter and I provided you with a list of topics as well. This is just very broad if you look at the list of topics for the whole question that cover many of the areas that were covered in the last strategic plan as well as things that have come up on the previous conference call including molecular pathways in autism, the molecular biology of genetic conditions related to autism such as rat TSC and fragile X, co-occurring conditions, development and developmental trajectories, immune and metabolic mechanisms, sex differences, neuro-anatomy and circuitry, cognitive sensory, motor

systems and functions, biology across the life span and research on biology underlying abilities which is in opposition to just the focus on disabilities.

Those are some of the things that have come out of the previous discussion and comments that were shared by email so can you think of any areas where significant progress has been made in some of those areas that sets us up for the next steps?

DR. REICHARDT: Technologically again I'd say – you say the mouse and rat models have been around but they're now some non-human primate models, also fish and IPS cells were particularly with IPS cells. The technology has developed tremendously and these are especially useful for future drug screening platforms.

In terms of rodent behavior I'd say there has been dramatic progress in basically the sophistications of which one can they analyze behavior and this is probably is still a significant deficit in human studies but there's a lot of potential because of the iPhone technology revolution. There have been some cases in terms of brain function, for example the Roswell set up paper where repetitive behaviors were localized and one synapse in the stratum I believe and the deficit. And so the impact off the genetics, the grand lens studies on neuro function have actually been quite revolutionary.

DR. KOROSHETZ: What's that last one?

DR. REICHARDT: The grand lenses, these endoscopes.

DR. KOROSHETZ: Yes, I know what you mean. Yes.

DR. FENG: I think that's a great point. I want to add a few things. I think the most significant advance – one of them in the last few years, the genetics have really paved the way. The genetic

discovery was supported by – especially by the science foundation. It really paved the way of – for the neurobiology to allow us a model and a study in neurobiology of autism. I think that's the biggest impact to the field is really in the genetics. And the second thing actually is also from genetics and the form a lot of model studied the (unintelligible).

Both model study and genetic study point to three major pathways that could potentially explore for subgroup of patients potentially for new (unintelligible) a lot of model to be (unintelligible) exactly and what type (unintelligible) of individual subgroups but also on modifying of one (unintelligible) a major pathway going to help us to go deep, to understand and (unintelligible). The third thing is probably what is reversible, what is irreversible. In the last couple of years we had a lot of studies now we start to understand what is the developmental defect, what is the functional defect that's reversible and finally I want to add I think from the functional studies, the major progress is actually not on the generally about generally how the way we understand autism.

A lot of individual symptoms are related to the behavior abnormalities. We said we have a much better understanding now compared to a few years ago about the neurobiology of the (unintelligible) behavior. Now people start to look at a sensory defect, we have some studies again gaining momentum in this (unintelligible). So these are individual pathways and probably we can potentially go ahead of develop individual treatment instead of try to understand the whole autism as a one problem, try to develop a treatment for individual symptoms which are –very debilitating that could help us to really start to make an impact with the patients in the near future.

DR. DANIELS: Thank you, additional comments?

DR. DAVIS: Could I add one? This is Gray. From my perspective I think that the work from Chris Walsh's lab, the impact of somatic mutations in the developing organism is profound and it's profound because it allows for a kind of two-hit hypothesis to impact either the severity or the risk towards any neuro-developmental disorder, something that I had never considered possible before until I had read about this recent work.

It also poses a grand challenge I think for the future which is that to understand and diagnose and even experiment with that kind of possibility is a new frontier. So understanding how thematically derived mutations could affect large clonal regions of the brain and impact to a disease is a kind of new area and something that I think is worth exploring.

DR. BATTEY: This is Jim Battey. I completely agree with that last comment. I think this is a scenario that many of us four or five years ago wouldn't have appreciated as being an important growth area for understanding the biology of this disease and our thinking is shifted.

DR. DANIELS: Great, thank you.

DR. REICHARDT: And the other paper that I would just cite would be Ben Neil's paper which is much harder to deal with the genetics but it deals with polygenic risk factors. So co-morbidity basically, co-associations with intellectual attainment for example, that was a major genetic paper, I mean – yes.

DR. KOROSHETZ: How about it applies to patients in terms of understanding the developmental ranges with imaging in infants, the changes in eye control in infants. Those are a little bit older but in terms of following patients and understanding what's going on in patients, anybody else have other things they'd

like to add besides things like imaging, eye tracking, crossover?

DR. REICHARDT: Binocular rivalry, the field barely lists – barely misses more objective majors of behavior in humans which would include eye tracking, binocular rivalry and imaging assessment, yes.

DR. REDCAY: So one thing I think on the human imaging side that's been notable recently is making these really large data sets, doing more large scale aggregation of resting state data for example, instructional MRI so we can actually get a more reliable understanding of some of these differences that we're seeing from these more small scale studies emerging in the literature.

DR. NORDHAL: I'd also add that there are several studies ongoing that I think will give us findings soon both on sex differences in autism so there's more of a focus on finding more females to include in our imaging studies. As well there are some ongoing longitudinal studies, particularly coming from the (IBIS) group. That I think will shed some light on some early brain markers on autism.

DR. KOROSHETZ: Using what technology?

DR. NORDHAL: This is imaging.

DR. KOROSHETZ: I see.

DR. NORDHAL: I'd like to highlight a paper that came out recently. The first author is Marchetto and they were exploring or finding the ways known about from the imaging literature of brain overgrowth and they used – they derived stem cells from individuals who would – who had this early brain overgrowth - individuals with autism - and were able to derive neurons from these to look at the actual mechanisms underlying early brain overgrowth. I thought that was a significant

contribution in moving towards into the patient population showing work that could be done.

DR. PELPHREY: This is Kevin. The paper that you were just talking about was out of Flora Vaccarino's lab. And we're following up with the patients with imaging technology to let us look at Gaba functions to some of the most important genetic (unintelligible) related to (unintelligible) imbalance so they're using imaging to go out there individual, pheno-type we have an understanding of the genetics from the genetics close approach to the imaging.

I think it's something that's going to be valuable. Then related to that I think we're (unintelligible) limited imaging where at the (unintelligible) systems level we can begin to project response to treatment. Say which kid will benefit from which treatment so the involvement of stratification biomarker and tools to allow us to understand why interventions work and when they don't work why at a systems level and then begin to think about how we can take as far as intervention.

Even though we're a group that's talking about basic biology we're at a new time where we can use the standard of care intervention as experiment with randomization to understand the biology of autism at the level of (unintelligible).

DR. NORDHAL: Great. And I'd just echo that the really important thing is being able to find brain markers that are going to predict treatment responses I think holds a lot of promise.

DR. PELPHREY: Yes, pretty sure. We got a – this is boasting about our own work but we have a paper in the works coming in, molecular psychiatry where we show that we can predict which kids will benefit from the behavioral intervention with a great deal of liability and furthermore why those kids. So for example that now becomes a target for

oncology to see if we can turn non-responders to responders.

DR. DANIELS: Any other comments?

DR. KOROSHETZ: I just had a couple of questions. Really trying to get the people know things about recent progress in some of these other areas. There has been a lot of interest in the immune system with regard to its role and development and there was a Geshwin paper looking at transcriptomic analysis of brain finding, immune pathways abnormal in autism that were not predicted by (G. West) studies. Does anybody of any other immune studies in terms of causative in terms of autism? There was a Beth Stevens work and that was schizophrenia. Anybody have any ideas there on immune system?

DR. REICHARDT: Some of the most interesting stuff is work like that's being done by (C.O. Palmer) at Stanford looking at interactions between genetic risk and immune system. I would guess a lot of the risk factors end up – the non-genetic risk factors end up interacting with genetic risk.

DR. DAVIS: Yes I'd suspect that too. And this is probably an area that's at – is going to expand and emerge in the near future. It's something that holds a lot of promise actually.

DR. KOROSHETZ: A couple of other questions. So in terms of particularly from sitting on ICC and hearing from the parents I was brought to the idea that it might be good to just think about what the major symptomatic problems are and try to state what we know and don't know about their basis. So we mentioned repetitive behaviors. The other things which come up which I know less about are do we know anything about the biology of the sleep disorders or the biology. Jim in terms of the language and communication problems which are prominent, anything new in those areas.

DR. BATTEY: Nothing that I'm aware of unfortunately.

DR. REICHARDT: I think there's – well not in terms of disorders but there's been tremendous work from Yin Dang and others on just identifying the circuits that are involved in controlling sleep for example which I think is terrific. I think one of the really underrepresented areas has been the function of the enteric nervous system which is probably important in the GI disorders.

DR. FENG: We have recent study with Mike Halassa lab at NYU publish it to identify pharmacally particularly nucleus which controls the sleep formation for developing disorder in mouse study and (unintelligible) compound that can correct the study in mouse study, published this year, just a few months ago in NATURE. HALASSA, H-A-L-A-S-S-A.

DR. REICHARDT: Yes.

DR. KOROSHETZ: Yes, I remember that one.

DR. DAVIS: One thing I'd add to all of this particularly when talking about specific phenotypes is moving forward, trying to not only understand the neurobasis for those phenotypes but understanding whether they're primary or secondary outcomes of the underlying cause and this gets back to an interest of my own which is the adaptive capacity of the nervous system. To what extent is the cause creating adaptive changes that then create further manifestations of the disease?

So understanding homeostatic or metaplastic mechanisms of the nervous system which are profound to the extent that those are creating sequalli that are tightly correlated but not necessarily causatively related to the underlying disease caused.

DR. KOROSHETZ: What examples would you throw out as something we could hang our hats on?

DR. DAVIS: What I would hang your hat on would be the kind of basic neuroscience from many different labs the capacity of individual nerve cells or neuro circuits to adapt to perturbations. So if the perturbation is a developmental alteration that shifts cells into a non-normal paradigm they have the capacity to move back and rearrange ion channel expression or synaptic strength and then attempt to restore normal function, to the extent that those – that adaptive change becomes maladaptive I don't think we know if that's plausible but it certainly is a possibility.

We do know the adaptive capacity of the nervous system is huge and we do know that there's a genetic basis underlying autism. We don't know to what extent these underlying mutations drive adaptive changes in the nervous system that then could impact all of these different phenotypes. I think that's another frontier that's worth considering.

DR. FENG: Yes I totally agree. That's a very good point.

DR. KOROSHETZ: Any neurobiological understanding of the savant behaviors?

(No response.)

DR. KOROSHETZ: No, okay. Then there are some things right about – and we know the language circuits and certainly language delay one of the key features. Do people know studies in autism that identify abnormalities in the auditory language processing systems that would be good to highlight?

DR. REICHARDT: Some of the auditory of vocal responses, Tim Roberts is doing.

DR. KOROSHETZ: Okay anything in terms of attention, abnormalities in the attention circuits? Clearly another big problem that the parents are seeing, wandering and another thing that comes up frequently to IACC is the problems of wandering so the behaviors, interesting when you think about them to try and understand what the final basis for them might be. Anybody has ideas on that?

DR. REICHARDT: I don't actually. I think that's really hard. That's one of the hardest things to address because it involves motivation.

DR. KOROSHETZ: Okay. The other thing that comes up are GI issues. So we mentioned enteric nervous system. We know more about it. Does anybody know of actual troubles with autism related to enteric nervous system? Has there been some – we talk about micro biome abnormalities? Doesn't resonate? Okay.

DR. DAVIS: Was there a background to that question like in terms of how that got on the list?

DR. KOROSHETZ: I had a couple of things I put on the list from being at the IACC over the years that the parents have brought to our attention as neglected areas to try and understand why these things are happening.

DR. DAVIS: And it's your impression is that this is coming from popular media attention to gut/brain biome or is this patient driven and phenotype driven?

DR. KOROSHETZ: I think it's phenotype driven. The things I've been – yes, phenotype driven.

DR. FENG: Yes. Some studies on the enteric nervous system dysfunction but nothing really break through yet. I think based on talking to

doctors and the family the phenotype is there. Symptoms are there. They're very significant to a subset in the patient but I don't –

DR. DAVIS: And what tend to be the symptoms? I'm sorry.

DR. FENG: A few studies but it's very preliminary.

DR. DAVIS: What tend to be the symptoms? I'm just curious.

DR. KOROSHETZ: The symptoms are mostly abdominal pain, reflux, sometimes bowel disorder, bowel constipation, diarrhea but abdominal pain seems to be the big one, not clear what it is. When studies have been done – there have been some studies done (using) autistic to controls and as far as I can see there's not a tremendous signal that they're more common but they present certainly in different ways in autistic kids.

DR. BATTEY: Yes but in the pediatric population chronic recurring abdominal pain is real common.

DR. DAVIS: Yes.

DR. KOROSHETZ: So it could be because of the problem with communication, things could get at a…

DR. BATTEY: Or it could be because the parents are more sensitive to what's going on with their children with autism.

DR. KOROSHETZ: Right.

DR. DANIELS: This is Susan. There's also food selectivity that plays into that and we do have Tim Buie on question 4 and so he's been addressing some of the clinical and treatment aspects of that issue.

DR. KOROSHETZ: Right.

DR. RING: This is Rob. I'd like to just reflect listening to the conversation and as we go through each of these co-morbid feature associated symptoms, whether or not you take sleep, anxiety, attention, GI issues, you name it. I think there are some important strategic dimension to thinking about this that should be part of the discussion.

Certainly as you think about study design a lot of the studies looking at any one of these symptoms are autism versus control and maybe not take anxiety for instance, anxiety and autism versus generalized anxiety in a typically developing non-autistic population. What really are the driving features differentiating the biology beneath those constructs between two populations and I think this is important from a strategic point of view too, just reflecting on where I was back at Pfizer heading the autism unit there.

We wanted to bring a compound forward for the treatment of what we were calling for the lack of regulatory pathway at the time anxiety associated with autism. We got a lot of pushback from FDA on the pseudo-specificity of a claim like that because we couldn't answer the question that came right back. So how does the anxiety in autism differentiate from an anxiety in a typically developing population beyond responsivity to specific classes psychotropic medications although they respond differently the SSRIs or benzodiazepines?

I think as we look at each of these associated symptom domains and try to prosecute questions about the underlying biology and what they might reveal about the origin of that symptom is connectiveness to autism itself but as we think about prosecuting it with an eye towards launching therapeutic development against those domains it's going to be incredibly important for us to

establish differentiation between that construct in an autism population versus that same construct in a non-autism population and not just autism versus controls.

I think that's being done and I'm not saying that it isn't but I couldn't emphasize the importance of that from a strategic point of view, otherwise a lot of the biology will be as you try to turn it into products, turn it into medicines and therapeutic technologies will be charged with some level of pseudo-specificity so just making that point from more of a higher altitude.

DR. DAVIS: Here's another way to emphasize that to suggest that prioritizing those fundamental pieces of biology that are most likely to be directly associated and how one would go about making those priority. I have no idea.

DR. RING: Yes. Along that theme I think it's just important for us to establish what's unique about those features and take GI symptoms. What's really unique about constipation or diarrhea or abdominal pain in autism versus the same symptoms that occur prevalently in typically developing kids or how asleep the disruption sleep architecture in autism is really different from the same disruption sleep architecture we see broadly and typically in developing populations.

That's already at the center but just emphasizing it more for down the road we're going to have to convert this, these findings into practice, reduce that to treatments and there'll be a regulatory conversation at some point. That'll be very focused on protecting the – avoid in trying to use autism as a preferred path to get treatments for sleep onto the market that may not be unique to autism at all. And so there's – there'll be that conversation at some point and it should define the way biology – the research is prosecuted now but it should be part of the discussion is really what we're arguing for.

DR. KOROSHETZ: I think the flip side of that if I got it right is that what occurs now is that conclusions drawn from research in typical developing kids is what's used to guide the treatment of kids with autism so that we don't really understand the unique features of autism so we're using the drugs that were really studied in typical developing people. Epilepsy is an example where we use the drugs for epilepsy and autism that we use in other kids with epilepsy without any knowledge about which one's more effective in autism versus non-autistic kids. I guess same thing with behavioral treatments. We're using drugs that were developed from a non-autistic and using them in the autistic population.

DR. DAVIS: I guess just one further comment on that. I think that makes some sense but it also – I think it also impacts how we're thinking about the funding process in general or the prioritizing things. The use of treatment for epilepsy for example in an autistic population could in fact be driven by the research in epilepsy.

DR. RING: Absolutely.

DR. DAVIS: And deciding where to devote energy and resource within the context of autism might not be best driven by studying epilepsy. That's the question that I also take from this, not only looking forward to where the treatments come from but also where the emphasis could be given a finite amount of resources.

DR. DANIELS: So we don't have Kasha on the phone today but she had some comments about progress being made in development and in developmental trajectories and especially understanding the underlying biology of autism at very early ages as early as six months and that potentially being able to lead to more work in earlier ages so she'll be able to share some of that in writing when we get to our writing task.

Is there something anyone wants to share on sex differences and where we are with that?

DR. KOROSHETZ: I thought that the most interesting stuff was the genetic lode differences being required to be higher to get autistic phenotypes in females as opposed to males. That's a couple years old.

DR. REICHARDT: And with the more recent study from Geshwin's lab, showing that there was differential expression of autism risk genes in the brain depending on sex suggesting there might be threshold issues.

DR. PELPHREY: This is Kevin. Dan is part of our autism network and so we are collecting (unintelligible) sequencing and imaging data on very large samples of girls and now planning on following them longitudinally and the additional data coming out from that. The lode issues that you see in genetics are also reflected and tend to be effectiveness of the brain system in autism as it gets to the same severity of autism. They have not only a higher genetic lode but also a more extensive hit on some of the (unintelligible) systems involved in social condition and social perception that has then been related at the core features of autism. And then quite uniquely in the theme of siblings which there are more of you see very nice what looks like complacentory processes that are – seem to be protecting them from expecting that genetic risk for autism. So all of that's preliminary and it's being – it'll be announced and it'll be coming out over the next…

((Crosstalk))

DR. NORDHAL: I would just add that we have an ongoing study where we're looking at younger girls with autism. We don't have published findings on that yet because the research is in progress. One of the challenges is just finding enough females to include in these imaging studies because there

are fewer of them so it takes a little bit more time to get equal sample size with the boys and girls. But I do expect that we will be sex differences in the brain in the coming year or so. We finally have enough girls to look at and compare to the boys with autism.

DR. DANIELS: Do we have any updates on aging with autism, in the biology of aging?

(No response)

DR. DANIELS: This is something that's come across third question areas.

DR. KOROSHETZ: I think there have been issues certainly that ICC brought up about hypertension, obesity leading to poor vascular health as people go into adulthood. Anything else you remember Sue? Those are the things I remember.

DR. DANIELS: I don't know if there are any publications on poly pharmacy and aging but that may also have an impact on some of those other indicators. I think that we've covered – at least talking about progress in some of the areas so now maybe we can turn the discussion to talking more about what opportunities there are and what we want to do in the future, which areas are really in need that are great opportunities but haven't been explored yet and need to be developed?

DR. KOROSHETZ: Okay.

DR. REICHARDT: Can I just say I think one need is to determine that which animal models are robust that's repeatable across species and across strains so that they can actually provide guides to use for future human studies.

DR. REDCAY: Related to that, I think having more collaborative teams doing translational work from animal to imaging to clinical applications

will be having a focus on that will help facilitate that.

DR. REICHARDT: I also think that the genetics has suggested some potential as included identification of some potentially drugable target such as the ion channels that one could imagine being used for targetive therapies for affected individuals if the right reagents were identified.

DR. KOROSHETZ: I've got a somewhat narrow view of things given a lot of work on the brain initiative that we have these new technologies coming out at a rapid pace to try and understand circuit abnormalities particularly in the animal models, that some of the behavioral aspects of autism – say like with the sensory or language or attention could come under a much more deep scrutiny than before.

In the human case I don't know of any technologies that are going to be applicable right away but there are some potentially coming down the road but wondering if there's something to be gained by trying to understand the circuit abnormalities with more emphasis on things like devote potentials, transmagnetic stimulation to look at things like intracortical or local connections in actual people to try and understand what the circuit abnormalities are.

The imaging, the connectome on project gives us a pretty good picture of the variants that we see at the MR level (Mizo) connectome, macro connectome and this currently a light span connectome project which is collecting data and kids of different ages. It's just very interesting to know what really stands up in the way of differences in terms of the connectome between folks with autism and typical developing kids.

DR. BATTEY: Well Walter that baseline data ought to be available going forward.

DR. KOROSHETZ: Yes.

DR. BATTEY: So that may be an opportunity for the future.

DR. DAVIS: I think I'd like to put in a plug for the importance of – I hear a lot of movement towards translation and certainly all of these things that are being discussed are extremely important but I'm still absolutely struck by the fact that we have this very complex genetic fingerprint that's emerging from (unintelligible) and remodeling factors to synaptic chains and to my read as yet there's no direct connection there.

I suspect that the eventual picture will be of tremendous complexity, not just signaling pathways and the idea that we'd already be considering it never hurts to try but the therapeutic intervention when we still are so far from understanding common underlying molecular genetic disruption seems to be putting the cart before the horse in a way. In some level underscoring the importance of the underlying biology seems to be essential.

DR. DANIELS: So what are the big opportunities there?

DR. DAVIS: I think there are big opportunities in exploring the kind of complexity of the underlying biology. I think there's a tendency because of the way science is often pursued for people to put in linear pathways and think linearly. I think this is the impact where systems' biology approaches may have a big impact not just on large data in terms of genomic profiling or other kinds of things but actually understanding the complexity of molecular genetic interactions among the signaling pathways, the ones that are primarily disturbed and the ones that are changing as a consequence.

These are complex cells and they're a developing system and we're looking at a developing system in compensatory motion essentially. That's ultimately likely to be directly relevant to this kind of neuro-developmental disorder. That's a very challenging problem and it may very well be that the best therapeutic approaches aren't directly related to the individual clause but the outcome basically would be treating the altered or adaptive or altered developmental brain rather than the cause that's genetic to begin with.

DR. KOROSHETZ: Yes. I think with the clinical translation the way I see it as the less you know, the lower the probability of success. Sometimes as you said you got to try things when there's a glimmer of hope but your chances of success are going to be quite slim without a full knowledge of the complexity.

DR. REDCAY: I think one thing I was referring more to just the translational, directly moving these things to the clinical domain is just having more interaction among these different levels so having more findings from one level inform the other, even if it's not ready for actual clinical implementation yet. But if you have more of these collaborate teams then you can be talking back and forth and inform each other of where the next place to go is.

DR. DAVIS: Absolutely.

DR. KOROSHETZ: Assuming from our institute, I'd just love to know what's underlying the epilepsy in these kids. Clearly that's a synaptic circuit dysfunction of high order magnitude. It's incredibly common. Sometimes it's very hard to control. Going after the epilepsy could potentially open up doors to what the synaptic problems are more generally as well. Sometimes focusing on a piece of it could change the way we think about things.

DR. DAVIS: Certainly.

DR. KOROSHETZ: So anything else about translating research into practice?

(No response.)

DR. REICHARDT: I'll just say I think that there are a few attractive targets that are emerging from the basic science that's been done and more may emerge in the future that remain that now are potentially drugable targets assuming the right drugs are discovered and developed.

DR. KOROSHETZ: Certainly from the more highly penetrant genetic assorters as potential ways are going about it, Tourette syndrome for instance.

DR. REICHARDT: Tourette syndrome is a reversible example, a good example, some of the channel where the mutations in channel and principles in drugs that may modulate channel function in appropriate ways. SCN1A I believe for example has expressed mainly an inhibitory neuron and there's a lot of mutations that affect it in a variety of ways.

DR. KOROSHETZ: Okay so anything else on the translation? So do we want to want to jump the barriers to progress? There's lots of barriers.

(No response.)

DR. KOROSHETZ: The funding is usually where people tell me on the phone except for Jim. Jim never talks about that.

DR. REDCAY: One thing just from the human imaging perspective that's been a barrier is we have relatively small studies and there's kind of becoming inconsistencies and a lot of these are cross-sectional designs so they become these patterns of maybe interesting developmental

changes for example in brain network organization and hyper and hypo connectivity. But this – they're not necessarily consistent if we don't have these really large scale studies where we have multiple collaborative teams looking at this together.

That's why I think what's notable is aggregating across a lot of different labs to come up with really large data sets where we can test these hypotheses but there's some issues with that large data set. There's a lot of variability on site because it's all done post-talk rather than going forward with having more consistency in the way that we're aggregating our data so we can have much larger data sets to be able to test these questions with more reliability.

DR. BATTEY: But that almost has to be done prospectively.

DR. REDCAY: Yes exactly. I think prospectively.

DR. BATTEY: That's very hard to retrofit after the studies have been done.

DR. REDCAY: So putting more emphasis on that more prospective approach.

DR. BATTEY: I would agree with that because it's obvious we're going to need a lot of patience to sort this out.

DR. KOROSHETZ: The other thing, it sounds like we're going in that direction about trying to move from court sectional to longitudinal studies so you can see the development play out.

DR. REDCAY: Exactly.

DR. BATTEY: Yes, that too.

DR. REDCAY: And there's a lot of good longitudinal. I think Christine just mentioned this earlier especially early on but also focusing those. I think this was noted in the public comment in later childhood and transition to adolescence and transition into adulthood, having longitudinal studies throughout.

Dr. Battey: Yes. I'd agree they're very important. They're very hard to do just because of the logistics of keeping patience and families and everything in one place for a long period of time is complicated.

DR. REDCAY: Yes. I completely agree. I'm just – we're really putting…

DR. BATTEY: They're really important. I'm not downplaying the importance at all.

DR. DAVIS: At a very different level that one of the barriers we face is the inability really to pursue quantitative cell biology in vivo, that we often move from genetics to circuitry in the organisms and behavior very quickly but it's very difficult to do the kind of quantitative causative cell biology which is normally done in a dish. And therefore in a very strange cellular environment to be able to do those kinds of kinds of studies in vivo and this is where tools from the brain initiative are likely to be transformative I think in the next ten years, allowing these kinds of probes and these kinds of studies to be done in the genetic models but in an existing neuro circuit. If I were to think of a technological barrier, that would be one.

DR. NORDHAL: I just want to echo Liz's comment about the large - the need for large sample sizes from - that are planned in advance rather than the retrospective, the by type networks that have happened. And just to illustrate that, we have a cohort of over 360 children in our study but if we find a subgroup that is sort of interesting in

about 15% of the kids, it knocks our numbers way down again. And so rather than thinking about sample sizes in the hundreds, we're probably looking at needing sample sizes in the thousands which is going to take integration across different sites.

DR. BATTEY: That's going to be especially true if the underlying cause of the disease is an aggregation of a bunch of small effects having a cumulative effective.

DR. NORDHAL: Right. And maybe adding there's a lot of strength in numbers in genetic studies, but I think there's also - the more that we can phenotype these kids that are individuals that we're collecting this genetic data from, the more information we can get from that.

DR. DANIELS: Anything else on barriers?

DR. KOROSHETZ: Let me just throw out the question of maybe just the old folks remember is the question of whether or not there are signature histologic abnormalities that we need techniques to quantify better to know if they're real or not. We're talking about the things that have been described in terms of cerebellum or synaptic density, what is the basis of the brain overgrowth at a certain developmental stage. Anybody resonate with that or not? Too old fashioned?

DR. REICHARDT: No, I think it remains valid. Everything that's all bad actually. Some questions just hang around forever.

DR. NORDHAL: I think there is promise in the idea of using (unintelligible) potent stem cells to try to get at these mechanisms. So getting back to that paper I was mentioning earlier, the Marchetto paper, using stem cells from individuals from autism to then - to derive neurons to see what's going on, on a cellular level, I think holds a lot of promise.

DR. REICHARDT: And I would add fish to that list. I mean since they play a similar role you can make - there is a certain amount of behavior and they can be screened in large numbers too.

DR. KOROSHETZ: I was thinking of applying the clarity technique to a fetal brain with a known mutation. Seemingly, you'd have the ability to really nail down what the architectural differences are like you could never do before.

DR. REICHARDT: I would agree and actually the expression on the single cell level, that's probably one of the most promising areas for understanding sex differences. I mean I think the genetic is going to be very informative not just in identifying genes but telling us when and where they act through enhanced or promoters, what's known about timing and so on. And it's - in principle, it's relatively easy to take early material from both sexes and systematically screen interesting areas of the brain at very high single cell resolution for expression.

DR. KOROSHETZ: The one barrier that comes up oftentimes is the accessibility of brain tissue for research. I know Simons has been working hard with NIH to try and solve it but do we still put that down as a major barrier?

DR. DANIELS: Yes.

DR. DAVIS: No question.

DR. REICHARDT: Yes.

DR. RING: Yes.

DR. DANIELS: Any other barriers? So then let's move onto the next question. What are some of the most pressing needs or evidence gaps that can be addressed through research given where we are now?

DR. KOROSHETZ: I think we've heard a lot about the promise of trying to do more intense studies with regard to the mechanisms related to the genetic abnormalities associated with autism. I think we heard the evidence gap of trying to look at development of the brain with the appropriate numbers of patients to be able to really nail down differences versus typical developing or particularly with different phenotypes of autism.

DR. DANIELS: Anything else that you think that hasn't been covered on previous questions in this area? All right, so then we can move onto the next question. Are there some emerging areas of research that you feel are prime for development that need additional support?

DR. DAVIS: Well, I would go back to the impact of somatic mutations and their impact on developmental lineages and disease.

DR. DANIELS: Any others that haven't been covered already in what we've discussed?

DR. BATTEY: So it's been mentioned before but well validated animal models would be a big help.

DR. FENG: Yes, I would second that. Without good animal models, it's really hard to dissect (unintelligent). It just cannot open human brains to study.

DR. KOROSHETZ: And do you think you have to have marmoset?

DR. FENG: Well, whatever the best. Marmoset is…

DR. KOROSHETZ: That was a trick question.

(Laughter.)

DR. FENG: It's still in testing. We have no proof that it will work better but it has not failed. That's all I have to say.

DR. KOROSHETZ: I guess one thing could be this issue of getting out of the rodent towards non-human primates certainly would people buy into that as something that needs additional support that you can look at different?

DR. REICHARDT: I would even say before doing that, simply showing the behaviors that are generalizable across every member of the same species. I mean this is one of the flaws of mouse research, right.

DR. BATTEY: Well, that's right. If you look at a whole series of inbred strains of mice and you look at a behavioral phenotype you can find quite a range.

DR. REICHARDT: Yes, in fact there's a recent neuron paper that showed that some of the behavioral phenotypes were contrary to each other. I mean this was in the F1 study with 30 different strains of mice and looking at two genes. And so when the behaviors are not consistent - robust enough to be consistent across mouse strains, the prospects for interpreting anything in terms of other species or humans just seems - it's a shot in the dark.

DR. BATTEY: Yes, I'd say it's unlikely.

DR. DAVIS: Is one of the underlying issues here that we've got a disease that's characterized through behavior but one would really like to have some other underlying cause that people would agree upon was directly related and whether that be physiological or imaging related.

DR. REICHARDT: And that has to be generalizable across species it seems to me.

DR. DAVIS: Right.

DR. BATTEY: Yes, I think we're talking about a biomarker now or better biomarkers.

DR. DAVIS: Or phenotype at some level, right?

DR. BATTEY: Well, that could be a biomarker.

DR. DAVIS: Absolutely, absolutely.

DR. REICHARDT: Well, phenotypes that are robust to genetic interaction basically.

DR. BATTEY: Exactly and that aren't affected by very subtle allelic variance, you know, such as what you find when you compare inbred strains of mice.

DR. DAVIS: Exactly.

DR. DANIELS: Other emerging areas that are worth mentioning?

DR. DAVIS: I still would mention the adaptive capacity of the nervous system, that homeostatic and metaplastic mechanisms in the nervous system are still something that hasn't really emerged yet.

DR. KOROSHETZ: I mean the other that gets to a little bit is the environmental experiential influences on development in autism…

DR. DAVIS: Yes.

DR. KOROSHETZ: …which then relates to what works in terms of therapy because there you're influencing the input to the organism for better function and so that's I guess - in simple terms, trying to take advantages of the adaptive capacity.

DR. DAVIS: Or if understanding it could then help - if there were a biomarker for that it might reduce the variance of the treatment effectiveness I guess is the best way to put it.

DR. FENG: I want to mention something related to this. So we all know autism, sensory dysfunction is a very major issue and we also from neuroscience, we all know sensory (unintelligible) develop a sensory experience is critically in modifying certain development of function. So understand how the abnormal sensory input and given the unintelligible) would be probably varying point in the autism and we don't have a lot of studies on that. We have studies on vision but how does the abnormal sensory function in the autism, which is very common in autism, eventually lead to the abnormal modification of circuits that will be eventually come out of the behavior abnormality. So how we make this link probably very important because many of our circuits and functions and connectivity are (unintelligible) modified by sensory experience.

DR. KOROSHETZ: that's a good point and it relates to the adaptive part.

DR. DAVIS: Yes.

DR. DANIELS: Other input on this?

DR. BATTEY: I guess the one other thing that I'd mention and I don't know if it belongs in this section or not but any disease where the prevalence has increased as fast as this disease has, has almost got to have some sort of environmental thing driving that increase. And I don't think unless I'm mistaken, I don’t think that's well understood at all.

DR. DANIELS: Right, and question three will definitely be getting into that more.

DR. BATTEY: I guess I'm on the wrong question again.

DR. DANIELS: That's fine. There is some overlap I think sometimes between these questions.

DR. KOROSHETZ: I don't know if you knew what drivers there were from the environment that would certainly…

DR. BATTEY: Well that's something that at least you've got some control over.

DR. RING: And this may have been mentioned earlier but understanding the gene environmental action as it pertains to ASD.

DR. DAVIS: Absolutely.

DR. DANIELS: Anything else here in this area? So I have some other questions that are more about…

DR. KOROSHETZ: Let me just throw one thing out if I can just to see if anybody bites. Back to the immune system and brain development. Does anybody feel that that's something that should be pursued in autism more? I mean there's a lot of stuff - again, we mentioned schizophrenia.

DR. REICHARDT: It just bothers me a bit that as opposed to schizophrenia, at this point I don't think any of the genetic risk factors have obviously implicated the immune system. I mean I…

DR. KOROSHETZ: That's correct, yes. But then in Geshwin's paper, he found very abnormal immune system pathways in the RNA in the brain.

DR. REICHARDT: No, yes I'm sure it's functioning. There's all the work on micro (unintelligible) complement, the stuff that's just in some ways it's just a little curious. But…

DR. DAVIS: I guess the way I would think about it, and it's still an open question in general I think related to immunity in the nervous system, is the extent to which the immune players, molecularly, are responding to insult or developmental change as opposed to being utilized for ongoing basic functions. We know from all the work in David Sweat's lab and David Baltimore's lab that are there are innate immune components, signatures, and learning, and things. But I don't think we have a sense of what these pathways are doing for day-to-day neural function and integrity. They may not always be there in an adaptive classical immune response or even an adaptive innate immune response always.

And so there's a gap there and that may touch upon what its relationship to autism could be if these signatures that (unintelligible) are seeing are real and important.

DR. REICHARDT: That's actually a major thing, what I'd just say the Simons Foundation supported the…

DR. DAVIS: Yes, I think that's a big open question.

DR. REICHARDT: I would agree with that.

DR. KOROSHETZ: Okay, so…

DR. DANIELS: Ready to move onto some other questions?

DR. KOROSHETZ: Okay…

DR. DANIELS: So we have a few on the list of topics, we have some different policy issues that have come up in previous discussions by the committee or by the working group in the strategic plans. These include inclusion of people on the autism spectrum in planning and conducting research, which is a topic that recurs, inclusion

of individuals on the high needs end of the spectrum or minimally verbal individuals in research, research outcome measures, quality of life outcome measures, replicability of research, and then research workforce needs are just some suggestions of potential policy areas that you might want to think about.

Have there been any major changes recently that have in the policy arena that have helped the field move forward to start with?

DR. KOROSHETZ: I think from my viewpoint, it's the collaboration between some of the nonprofits and the NIH has certainly been moving things faster.

DR. BATTEY: No, I think that's been very productive.

DR. KOROSHETZ: I guess the replicability issue came up a couple of times. We started talking about animal models and throwing also small sample sizes of patients makes it harder to know whether things are real or not. I'm having a little trouble, Sue, in trying to figure out how the policy issues really relate to question two very much.

DR. DANIELS: So in the new law, we're required to address services and policy issues in the strategic plan. And so we were just trying to come up with some policy issues that might relate to basic research that - so that's how they would relate here. But if there are other kinds of issues that you think come up, you can feel free to raise those. These were a few of them and I think that on the past call you talked about replicability of research and that versus duplication of research. And there have been concerns raised by the government accountability office about duplication of research. And the last time this group talked about the importance of making sure that you can replicate research.

DR. BATTEY: I'm going to speak out strongly for the importance of replication and reproducibility, especially in behavioral studies.

DR. DAVIS: Here, here.

DR. REICHARDT: Yes.

DR. BATTEY: I don't know that the GAO always ever performed a behavioral study.

DR. KOROSHETZ: Well, I think they've done some bad behavior.

(Laughter.)

DR. BATTEY: They've certainly been guilty of some bad behavior.

DR. KOROSHETZ: So one policy issue might be - we mentioned the development of teams. Would that fall under policy?

DR. DANIELS: Sure.

((Crosstalk))

DR. BATTEY: …longitudinal studies, being able to put up the money over a long period of time to do long longitudinal follow-up studies.

DR. DANIELS: Is there anything we have right now that can be built upon to enable that?

DR. KOROSHETZ: I think the ACE Centers do some of that, sure.

DR. DANIELS: How about inclusion of people on the autism spectrum and inclusion of, especially of people with high needs or minimally verbal people in research. Any thoughts about that, if we've made any progress on that, if there's still

needs in that area? That seems to come up quite a bit in the committee.

DR. NORDHAL: Well, I can say something there on the imaging end is that historically, people with minimally verbal or self-injurious behavioral are often excluded from imaging studies due to compliance issues in getting the scans. And we recently published a paper on very effective methods, enlisting the help of trained behavior analysts to help MRI researchers include these types of individuals in our research studies so that we can get a better understanding of what's going on across the entire spectrum and not just on the high functioning kiddos that can climb into the scanner and be fine with it. So there is progress on that front I think.

DR. KOROSHETZ: Is that published?

DR. NORDHAL: It is published, yes.

DR. KOROSHETZ: That would be great.

DR. DANIELS: Yes, so we can cite that. So in terms of the research workforce for basic biology and autism, are there any particular needs, areas where you've seen needs for more development, whether it's interdisciplinary research, position research, or any area that you think needs more emphasis?

DR. KOROSHETZ: I would go maybe I think Lou mentioned right in the beginning was bringing in kind of the more of the engineering types to be able to assess particular behavioral issues with devices. So it seems to be an area that might give us some insights in terms of, say, monitoring a child over years in a room - in a house that's got cameras all over it and then analyzing interactions with people versus objects. Those types of behavioral assessments where you can integrate behavior over time would require

bringing in a new type of - more of an engineering group.

DR. REICHARDT: Better language - automatic language processing would help tremendously. This would be a huge asset for potential therapies.

DR. KOROSHETZ: These are primarily for phenotyping.

DR. REICHARDT: Yes, in principle it's a quantitative assessment of severity of disorder, monitoring of changes as a result of either behavioral or pharmacological interventions. Probably important for the lifetime studies, too.

DR. DANIELS: Anything else you can think of related to training or workforce? So then let's turn to the aspirational goal. So each of the questions in the strategic plan has an aspirational goal that was set as a long-term vision for what research or in some cases services in these areas will achieve.

So the aspirational goal for question two is currently worded as discover how ASD affects development, which will lead to targeted and personalized interventions. Do you think that this aspirational goal is still appropriate? Are there things that do you think you would like to change to broaden, or narrow, or otherwise change about the aspirational goal and where this field should be going?

DR. REICHARDT: I think it's hopelessly broad personally. I mean first of all many different disorders, I would say an aspirational goal would be to develop in biology to identify one or more promising targets that could be used to - for future therapeutic development, treat the disorder.

DR. DAVIS: The only thing about that, Lou, that I worry about, is the narrowing of focus,

which I don't think we're advanced enough yet to risk.

DR. REICHARDT: Okay. Well, then I think at least then the original goal should be pluralized I guess is what I should say. That's all. (Shank mutants) fairly don't act at the same stage and pathways as CHD8 mutants and so on. So yes.

DR. FENG: I think it should be broader.

DR. DANIELS: Are interventions the only goal for this area? Are there other things now as the field has developed that you think are possible goals of basic biology besides interventions?

DR. REICHARDT: I mean I think for IACC, I mean obviously changes, appropriate changes in society to make society more accepting and more beneficial and life more worth living for individuals with autism is really important but it seems to me that's beyond the scope of the biology.

DR. DAVIS: Could the scope be as simple as gaining sufficient biological understanding of the disease to drive future interventions and education?

DR. REICHARDT: I think that's pretty good actually.

DR. DANIELS: So I think in this context, interventions would include educational interventions. But were you talking about education like education of the public?

DR. DAVIS: Both actually. I was talking both about education of the children with autism but also educating the public about the underlying disease and that would impact things that Louis was mentioning about the way society interfaces with the autistic kids and families…

DR. DANIELS: Any other…

DR. DAVIS: …and that you can create a biological context that's understandable that would help.

DR. KOROSHETZ: Okay. I think this one is going to be something that we probably need to wordsmith.

DR. DANIELS: So I was just trying to get some different ideas here and then we can always work on this offline a little bit and discuss it on the next call. But are there any other thoughts that come to mind for anybody about the goal? So the idea of potentially expanding it a little bit to say something about biology informing society about the nature of autism.

DR. KOROSHETZ: I still think that the aspirational goal related to the biology, trying to understand the basis for the burden of illness that's experienced by people with autism that will hopefully lead to better treatments. At NIH, the missions are always that twofold, understand and then lead to treatments.

DR. BATTEY: But even just the understanding itself is a major step forward.

DR. KOROSHETZ: Yes, they’re both two parts.

DR. BATTEY: And everything else.

DR. RING: This is Rob. I'll apologize. I stepped out momentarily if this was already discussed but certainly, all of this doesn't necessarily funnel down towards intervention that prevention may also be a critical downstream creation of value through all of this.

And so for example, if indeed we find out that the mechanistic exploration of autism ideology reveals indeed there are environmental insults that are responsible for specific subgroups,

subtypes in this emerging ontology of understanding of the autism. If we know that indeed there is environmental risk for certain genotypes, this all could pay off in prevention and not just intervention.

So that could give us actionable risk factors that could shape other dimensions of public policy.

DR. BATTEY: I agree with that completely. That's something, A, that we can control and B, that makes sense given how rapidly the prevalence has been evolving.

DR. KOROSHETZ: And an early intervention could - intervention at an infant stage could also lead to prevention of (unintelligible).

DR. BATTEY: Like preventing an environmental insult for example.

DR. RING: Or even if we understood that certain inborn errors in some metabolic pathways increases risk and would that really be an intervention, a treatment intervention, or would that be a preventative move to develop therapeutic nutrition aimed at that? So I think in some ways capturing the enabling of prevention through basic understanding of biology should be part of that.

DR. KOROSHETZ: And I think also the other things that we think about are disease modification, trying to attenuate the progress of the disease and the severity. The other one is symptomatic benefit, which I think particularly for the parents around the table at the ICC, the pendulum in their families has swung to what they're most interested is understanding what's the root cause of the symptoms and how best to intervene to reduce them. So the symptomatic part I think is good to keep in.

DR. BATTEY: Absolutely. But even just being able to predict and give the family some idea of what's coming would be very - I think would be very valuable.

(Long pause.)

DR. KOROSHETZ: Maybe we have to take a shot at wordsmithing this and send it around, and that's usually the way it comes out in the end. It's okay - I didn't hear anybody resonate with refining it to development. So is that - confining it to development. So we can - do we want to just let that go, the word development?

DR. DAVIS: Yes, I think that would be appropriate?

DR. REICHARDT: I think all of life is a development I'd say actually.

DR. KOROSHETZ: Well, I wish I was still developing.

DR. REICHARDT: That's not always in good ways.

DR. BATTEY: We're all developing, Walter, just at different stages.

DR. KOROSHETZ: I'm going, whatever the opposite of developing is that's what I'm doing.

DR. BATTEY: Well, I didn't say it was unidirectional.

DR. DAVIS: It's regression.

DR. KOROSHETZ: Speaking of regression, does anybody have any knowledge of understanding these regressive episodes that have been talked about or the fever associated with improvement? Those other things that come up, biological basis of regression.

DR. REICHARDT: I don't think so. I would say that a fever is of some interest to Simons and we are sponsoring studies on that since there are - it's really now quite a bit known about what are the, again, neurons and circuits that control temperature response in the body and it's possible to manipulate them separately from the various cytokines and so son.

DR. KOROSHETZ: You haven't heard anything about the regression? What's going on there?

DR. REICHARDT: No. Yes, I just don't know. It's the kind of thing - if the American health system weren't so balkanized. I mean if everybody in every part of the country collected the same information then you could do the same - you could do really meaningful environmental studies, toxicology studies, behavioral studies. This is one of the big problems we have.

DR. DANIELS: So we've collected a few ideas about the aspirational goals. I think that we can work on that offline and by next time have some ideas about what we can do with that. With the chapter title, does anyone have any concerns about how it's currently worded, how can I understand what is happening, which was meant to be a consumer based question that would describe why we're looking at the underlying biology. So are there any suggestions there or are we comfortable with how it is now?

DR. KOROSHETZ: Anybody else changing their title?

DR. DANIELS: I think that there might be one or two groups that might make some minor changes in theirs.

DR. BATTEY: No, but I like this one. It's plain language.

DR. REICHARDT: Yes.

DR. DAVIS: I agree.

DR. DANIELS: All right. Well, then I think that we've gotten through everything that we needed to do on this call. After the call, I'll be working with the chairs to develop an outline for the chapter and the chairs will be contacting members of the working group to get some assistance with drafting certain parts that might be related to your expertise. We're going to be trying to fit information about this update into ten pages or less and it's supposed to be lay friendly.

So we will certainly rely on citations of research rather than extensive descriptions of all of the findings, but we'll want to highlight the most major developments and then areas that you think are the most promising for future work. On the next call, we'll be talking about developing objectives for this chapter and in the past, across the whole strategic plan, we've had 78 objectives. And in the committee in the last discussions decided that they would move towards a new strategic plan with about 20 to 21 objectives, which would be a lot more manageable.

And so for this chapter, it will have three objectives and they can be broad objectives that will capture a number of different themes. And then underneath each objective you can have examples of the kinds of work that would be responsive. And so you can be thinking about what you think are the major areas that you might want to target with objectives and I'll be sending out some emails about that and our next call we can talk through what your suggestions are for objectives. Does anyone have any questions?

DR. KOROSHETZ: Remind us of the timeline.

DR. DANIELS: So we - the goal was to get the working group's work all finished by about

December, by the end of December. But I know that I've talked with some other working groups where they felt they had certain time constraints now and would have more time in January. And so they wanted more time after December to work.

So we will try to have the best draft we can have available by the next - by the January meeting of the IACC, which will be on January 13. So that gives us a fair amount of time to work on this draft chapter. So we'll be sending out information to those working groups. I'll work with the chairs on first developing an outline and then hopefully we'll have several weeks for people to contribute to the draft. So we really appreciate everyone's time and all your input during this call. And we will be posting a transcript of the call on our website and we'll be in touch about next steps. So thanks everyone for your time.

DR. DANIELS: Thank you.

GROUP: Thank you.

(Whereupon, the conference call was adjourned.)