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INTERAGENCY AUTISM COORDINATING COMMITTEE

SUBCOMMITTEE FOR
BASIC AND TRANSLATIONAL RESEARCH

STRATEGIC PLAN QUESTION 2 PLANNING GROUP

CONFERENCE CALL

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The Planning Group convened via teleconference, Walter Koroshetz, M.D., *Chair*, presiding.

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PROCEEDINGS:

Ms. Gemma Weiblinger: Okay, thank you very much. Hello, my name is Gemma Weiblinger, as the operator said, and I'm temporarily acting as the designated Federal official for Dr. Susan Daniels, who is currently out on maternity leave.

Welcome to the conference call to discuss the update for Question Number 2 of the Interagency Autism Coordinating Committee Strategic Plan from 2011, "How can I understand what's happening?"

I will now turn the call over to Dr. Walter Koroshetz, who will lead the discussion.

Dr. Koroshetz?

Dr. Walter Koroshetz: Thank you very much, Gemma, and thanks everyone for getting on. As Gemma mentioned, this is the group that is looking to update the IACC Strategic Plan on Question 2.

And why don't we go around and people

introduce themselves so that the listeners understand who we are, where we're coming from. So this is Dr. Walter Koroshetz. I'm the Deputy Director of NINDS and a member of the IACC. Carlos?

Dr. Carlos Pardo-Villamizar: Carlos Pardo from Johns Hopkins Department of Neurology.

Dr. Koroshetz: Great, thanks. And David?

Dr. David Amaral: I'm David Amaral. I'm a professor in the Department of Psychiatry and Behavioral Sciences at UC-Davis and the Research Director of the MIND Institute also at UC-Davis.

Dr. Koroshetz: Great. And anybody else? I think we're still waiting for Dennis Choi to join and Kevin Pelphrey, who's in Belgium, hopefully being able to join the call.

So just to sum up: What we did on the last call is we went through the Strategic Plan and separated out into multiple subtopics the issues that have previously been discussed as relevant to Question 2. And

then we assigned each of these subtopics to individuals in the Subcommittee. And each of those have submitted drafts of what they believe are the most important items to be included in the progress session, what have we learned in the last year, and also indicated to us what they think are the new gaps.

And so today's call, what we'd like to do is to take a look at the submissions, have those who prepared them kind of summarize for us why they picked what they picked. And I think at the end of the call we'll certainly have a better sense of what the major advances on Question 2 have been, what the new gap areas are.

We do, as we can see from the submissions which we certainly expected is that we are going to have to do some significant synthesis, some cutting down on words to hit our word limits for the update. But we certainly have made a lot of progress, I think, from reading the submissions, and I

think we have a lot of material that we would need to just kind of fashion a really good, high-quality update to the Strategic Plan.

So, I guess just to break the ice, I'll go first. So I was assigned the topics that had to do with the advances in molecular basis and the phenotypic autism. Basically, I think that there has been a tremendous amount of progress, certainly not – we haven't solved the problem – but compared to where we were, I think there's been a lot of progress in what's come out in 2011 and 2012.

I basically was struck by the fact that the previous work in autism, a lot of the progress was in identifying genes associated with risk of autism and genes that are causative in terms of the monogenic, highly heritable syndromes of autism such as Rett, Fragile X, and tuberous sclerosis.

So my write-up basically recounts the very high-profile papers that have uncovered some of the underlying biological effects of the genetic findings in autism. For instance,

I highlighted a discovery that if the TS1 tuberous sclerosis gene is deleted from the cerebellum in that animal model, the animals developed autism-like symptoms.

They did a pathology in the cerebellum, and many of these are ameliorated by the drug rapamycin, which is currently in trials of patients with tuberous sclerosis. It went into trials to look at its effects on the tumors in tuberous sclerosis, but this as well as other studies – for instance in the epilepsy world – are wondering whether there's a common pathway that can be intervened with rapamycin that would help a lot of the symptoms, including the autism symptoms. So I thought that was – that was why I highlighted that one.

I also talked about the work that's coming out of a number of different labs looking at the kind of yin and yang between Fragile X syndrome and tuberous sclerosis, where one you have increased protein synthesis, the other one you have decreased

protein synthesis.

And for some reason, which I don't quite understand but seems to be a consistent finding, is that GluR5, glutamate receptor 5 transmission is altered in both of these conditions. It's upregulated in one, downregulated in the other, but the idea is that it could be over- or under-activity; it could be an essential biological contributor to the symptoms in autism. And there are drugs that are being used in Fragile X to mediate the behaviors. And so that was also an underlying theme – again, close to at least pointing to potential therapies. And that's why I point that out.

There was one which I think overlapped with, I think, one of Kevin's, and that is the net risk allele was found to modulate brain circuitry. Kevin brought up the same paper when he talked about advances in circuitry, so that's a chance to bring things together there and save some space.

I also talked about some of the work

that’s come out with regard to the large synaptic complexes Shank and ProSAP, where mutations have been identified in large GWA studies and now have been shown to have some biological effect in animal model studies.

And finally ended up with something that maybe overlaps a bit with Carlos as well is the study looking at transcriptome in the brain – brains of persons with autism versus controls showing one interesting thing, which was the fact that in the controls there was a great deal of variability between gene transcription in say temporal and frontal lobes but that was absent in the brains with autism, which I thought was a very interesting finding.

The other one which overlaps with Carlos is the fact that in looking at the transcriptome in the brains of persons with autism versus controls, they found modules in synaptic proteins which correlate with and confirm what’s been previously seen in a lot of the GWA studies. But they also found a

module related to immune function in the brain, and this is potentially very interesting, given the last year findings from basic science showing how the immune system is sculpting synapses in the brain in development. So those were the kind of things that I thought were the most impactful biological discoveries in terms of a molecular basis and the syndromic autisms.

So a lot of cutting I have to do. But people have comments on those or things they think that I left out or maybe misinterpreted?

Dr. Pardo-Villamizar: I'd like to take the last part on the transcriptome analysis of brain tissue. I think that may go very well in the molecular pathways and also may be highlighted also at the connection between the immune system and brain development or brain function. Because I think that one of the findings of that paper by Geschwind is the prominence of immune-related genes in the transcriptome of those brains of patients

with autism.

Dr. Koroshetz: Right. So I think we can certainly, you know, you kind of brought those same points up, so I think when we get the language straight we'll combine those two ideas.

Dr. Amaral: Walter, this is David. Another thing that that paper highlights is the importance of post mortem material for advancing autism. And since Alison is not here, I'll just put in a word for the fact that I think that paper was 5 years in the coming or maybe even longer, primarily because there was so little resource.

And so, given that some of the expression differences that were reported in that paper actually not seen in blood, that it really highlights the importance of analyzing genetic changes in the autistic brain rather than in peripheral tissue.

Dr. Thomas Insel: David, this is Tom Insel. We had a conversation this morning on Question 7, which is the infrastructure

piece, and talked a bit about the brain collections and especially the dire state of the repository, with the loss of the tissue from the freezer meltdown in Boston earlier this year.

One of the things that would be really important to emphasize maybe in this section – and we'll catch it again in Chapter 7 – is the critical need for more tissue, better tissue, standardized collections of tissue.

And it's even I think more urgent, because as you say we're picking up these expression differences that don't show up in blood; we're picking them up in brain. But the increasing number of papers that are coming out in other areas suggesting an enormous amount of somatic variation would tell us that we may never get the most important signals from looking in blood. We will have to go to the affected tissue.

I don't know if we want to go there for this summary, but there is this to me amazing paper from Chris Walsh's lab that came out I

think in – earlier this year. I can't remember if it's January or February in *Neuron* about the hemimegalencephaly that's driven by somatic mutation that's only found in that side of the brain that's overgrowing and doesn't show up in the rest of the brain – certainly doesn't show up anywhere in blood. So it's kind of proof of principle that we need to be thinking about that as a possibility.

Part of why it's so tempting is that we learned from oncology that some of the best drug targets are actually not those that you pick up in blood but those that you pick up as somatic mutations in the tumor of interest. So this is all just to emphasize David's point that we must have much better collections of tissue of the affected organ.

Dr. Koroshetz: I think we can put that in the new gap areas. I think that would be the place for it, right, Tom?

Dr. Insel: Yes, yes. I think – and this is one of those places where it's actually

we’re worse off now than we were a year ago because we’ve lost so much tissue. And we didn’t have even 10 percent of what we needed then. So this is really a crisis I think for the field, especially for this chapter, to understand what’s happening in the brain. If you don’t have the brains to study, you’re pretty limited.

Dr. Koroshetz: Absolutely.

Dr. Pardo-Villamizar: This is Carlos Pardo from Hopkins. As a neuropathologist, I do agree 100 percent with those statements.

One thing that probably – if in the meeting is to make emphasis the need of information about brain banking that is – there is a lot of misunderstanding about the meaning of brain banking, particularly when there is dead or patient that died. So families – and even practitioners and even the pediatricians – are not necessarily making emphasis in tissue collection because there is a lot of ignorance on that issue.

Dr. Koroshetz: Okay. So why don’t we go

on? Carlos, do you want to?

Dr. Pardo-Villamizar: Sure.

Dr. Koroshetz: Since we ended up with the immune system, maybe we could start with the immune system.

Dr. Pardo-Villamizar: Yes. So I was assigned two areas. One is biomarkers, and the other one is immunity.

On the issue of biomarkers – at least in the last 12 months – there has been not necessarily a very good amount of papers or publications dealing with the biomarkers. And I think that this is another area in which there is a lot of frustration, because I mean we have been collecting a lot of blood, et cetera, but we don’t have really very good use of the blood.

And many of the studies are very limited, particularly because are very – are based – in a very small population of patients. And are really very – etiologically are unvalidated studies. So I think that unfortunately we don’t have really a good

report on what has been done in this area in the past 12 months or past couple of years.

So that is another area that probably we may need to emphasize a little bit. And the summary is that basically only one paper that was from a European group tackled the issue of studying plasma and some biomarkers in plasma use in proteomic techniques. And again, the outcome of that research is not necessarily very helpful for ratifying any fingerprint for autism or any of the associated disorders.

On the other hand, the progress on immunological factor has been very fascinating, and those are coming mostly from animal models. And the most important contribution last year was perhaps the additional demonstration that microglia play a critical role in cortical modeling and is perhaps a very important factor for establishment of the brain connectivity. And the work by Beth Stevens is perhaps the most important one that needs to be cited there.

The second aspect is the potential role of adaptive immunity. And I think that the animal model work that Patterson published recently in *PNAS* is something that highlights the issues of maternal and environmental factors, in particular immunological activation in mothers that may influence the immunological outcome in the littermate or in the offspring of these [inaudible comment] exposed to these maternal immune challenge.

And I think that that again is following in the direction that the maternal environment and the immunological challenge eventually may affect brain development and future behavior.

The second piece on animal models is coming from the MIND Institute and UC-Davis in which the passive transfer of maternal autoantibodies in a rodent model produced abnormalities, behavioral abnormalities. And I think that that is another important piece for understanding the role of the immune system on brain development and potential

pathogenesis of autism.

So I think that the third piece of information is coming from human studies. I think that perhaps one of the most prominent ones is coming from the Danish group using blood spots to demonstrate the presence of some abnormalities in the cytokine-chemokine network.

And again, this is probably resuscitating some of the studies that were done many, many years ago at NIH by Dr. Nelson, that pointing out the potential role of cytokines during brain development.

And the last piece of information – that is just a continuation of research that has been done before – was from the Paul Ashwood's group, that pointing out that some of the abnormalities in immunoglobulins that had been observed in patients with autism are not necessarily associated with B-cell dysfunction and may be associated with a more complex dysfunction of the cell network in the immune system.

But I think that the most prominent aspect – at least from my point of view – is what has been done in the animal models and particularly with the role of microglia as a very critical factor in building of the cortical organization and neuronal connectivity in the brain.

Dr. Insel: Carlos, I don’t know the Danish newborn study very well. The finding of decreased cytokines and chemokines – was that unexpected?

Dr. Pardo-Villamizar: No, actually, well, the paper is interesting, and I think that we need to cite that paper because I think that we need to revisit that ourselves in the prospective studies that have been done and have been funded by NIH.

Because there are some methodological issues that need to be revisited, particularly because these studies are based on blood spots that may be subject to a lot of problems, particularly degradation. And we never know if that lack of detection of those

cytokines is the result of degradation of the cytokine during the acquisition of the sample, processing of the sample.

But it points out that it's very possible that autism as a systemic disorder may affect in some way the development of the immune system. And the decreasing of some cytokines may reflect the presence of a hypoactive immune system. Again, I think that probably is an issue that probably needs to be examined with more detail and probably more carefully from a technical point of view.

Dr. Insel: Because as I understand this, and I don't know this area so you'll have to just clarify, it seems like most of the animal work was predicated on the idea that there's an immune stimulation or an immune challenge during pregnancy rather than a reduction in the inflammatory processes.

Dr. Pardo-Villamizar: That's correct. That's absolutely correct. Again, that's the reason I stated that there are some technical

issues and perhaps some potential pitfalls on this type of research coming from the handling of the samples, et cetera. And it's something that we need to revisit likely.

Dr. Koroshetz: Do you think, given the caveats, Carlos, and if we need to cut space, that maybe that – those kind of studies we could not include? Or do you think it's important to kind of raise the issue if we have kind of partial knowledge?

Dr. Pardo-Villamizar: So I think that – I mean, in terms of scientific weight of the paper – probably there is not too much weight of those observations because the potential pitfalls on the methodology.

However, for future research I think that the assessment of the fetal immune system and the neonate immune system is something that we need to focus.

Dr. Koroshetz: So that could go into like a gap area.

Dr. Pardo-Villamizar: Right.

Dr. Koroshetz: You bring up the fact

that we have some interesting findings but they're hard to – they're hard to know what to do with.

Dr. Pardo-Villamizar: Right.

Dr. Koroshetz: Okay, got it. David, do you have anything to add there?

Dr. Amaral: No, I think that Carlos did a good job covering the immune system.

Dr. Koroshetz: Great. Okay. Do you want to talk about the neuropath and the circuits?

Dr. Amaral: So I was assigned brain structure. And I presumed that it was going to overlap with the neurocircuitry that Kevin did. So I start out by trying to review papers dealing with MRI analysis of brains in autism. I point out that there were probably a couple of hundred in the last year and a half or so. And so it's certainly an area of active research.

A couple of trends: One is that there now are starting to be some papers coming out looking at early or potential early alterations in the brains of children that

are siblings of children with autism and therefore at high risk for a diagnosis. Several of these papers are coming out through the IBIS Network.

And the summary that so far looks like at very early ages, at 6 months there's nothing that is obvious in terms of brain volume changes or obvious other sort of region of interest changes in the brains.

But there are emerging studies that if you use diffusion tensor-weighted imaging and start looking at the integrity of fiber systems in the brain, there are at least a few papers – by Weinstein et al. and Wolf et al. – showing similar alterations in the diffusion parameters of the fibers.

So I think there's a trend now from looking at one part of the brain at a time to looking at large networks of fiber connections. And so in older individuals with autism, there have been a couple of papers that have tried to focus in on putative brain regions that are associated with social

behavior. And those papers have shown, using resting-state functional imaging, that there seems again to be some differences in the network characteristics of these brain regions associated with autism.

So at this point, I think it's a little bit early stages, but I think the advances – that rather than looking at one part of the brain at a time – people are trying to look at the integration of many, many brain regions at the same time that are associated with the diagnostic features of autism. So I think that's an advance.

The other thing that I – sort of on a more global level – that I detected in the literature from the past year or so is that people are using imaging with larger samples to try and define neural phenotypes. One of them that's interesting is there have been hints over the last several years, and there's a paper that was published by Fumiko Hoeft from UCSF suggesting that if you take a large number of characteristics of the

morphology of the brain of an individual with Fragile X and you compare it to individuals with idiopathic autism, that they actually can be – they are quite distinguishable. And so I think that that's an important distinction to make now because of the very well-deserved interest in the clinical trials of drugs that are associated with Fragile X or for the treatment of Fragile X and the implications for how they might be used for idiopathic autism.

And there's other – there's actually been work done here that, for example, showed that one of the common features of altered morphology of autism – that is that there's precocious brain growth. That keeps getting replicated over and over again. But when you look at a large population, you find that that only defines a subset, and in the study that came out of the MIND Institute, it was about 10 percent of boys that had the precocious brain growth, but then the vast majority of boys actually didn't show that

feature.

And what was interesting, which highlights one of the things that Kevin mentioned in his write-up, is that girls didn't show precocious brain growth. And so the sample of girls was smaller. But if that feature, which again is a sort of highly publicized feature of the biology of autism is only one that applies to boys – that will be interesting.

And as I was reviewing the literature, I came across a paper. And I have to read it more carefully, but what was interesting was there was a group in Israel that looked at MRI of Israeli patients with autism and found that – or they didn't find – that there was macrocephaly at all. So the claim that, perhaps due to a different genetic background, you don't see that biological feature of autism, and perhaps that subtype of autism doesn't exist in that ethnicity and culture.

So that's about all I contributed. And

then I think that this dovetails with what Kevin wrote. So there's probably plenty for the MRI side of things.

On the neuropathology side of things, it's again very modest what has come up over the last year. I think there was a sort of highly publicized paper indicating that perhaps the substrate for the enlarged brain was an increased number of neurons in the brains of individuals with autism. But then there was a second paper that came out a little bit later that carried out a very similar kind of study and found that there was in fact no change in the numbers of neurons in the frontal lobes of individuals with autism.

So, my conclusion there is that unless there's adequate tissue, as Tom was saying, to replicate studies and carry out these kinds of studies with a larger number of samples, it's hard to know. There's going to be little clarity on the cellular pathology of autism.

I didn’t see a lot else of note in terms of cellular characteristics from neuropathology.

I was also asked to look at some of the clinical subtypes. And I need to do more work on this. I haven’t quite finished this. But I thought a couple of things of note:

There was a meta-analysis by Barger et al. that looked at the issue of regression. And I think it’s important to point out that not too long ago, people were still arguing about whether regression really existed. And this study, which I think reviewed something like 30,000 subjects with autism found, that there is a consistent percentage of regression depending on whether it’s regression of language or social ability or both.

But the bottom line is that they found that 32 percent of individuals with autism have gone through a regressive trajectory, which takes place at about the end of the second year. So I think that that’s

interesting because again it defines I think a phenotype of autism or a trajectory of autism that we should be spending more time trying to understand what differentiates those individuals who have a regressive course of autism from those who have an earlier onset.

And I know that there's been a big effort in terms of looking at nonverbal individuals with autism. I'm not sure if I found any papers, and I need to consult with colleagues to see whether that has realized any kind of conclusions at this point in time as a phenotype – nonverbal autism and what're the distinctions beyond that.

The final thing was just developmental delay. And again, I think here the point is that there has been a sense that over time the amount of developmental, or comorbid developmental, delay in autism has been going down. And it would probably be – the most recent CDC surveillance report that came out suggested that comorbid developmental delay

was about 38 percent, which is substantially lower than figures that you see in the literature for 10 years ago or 20 years ago where it was closer to 60 or 70 percent. So, it seemed to me that that would be another important thing to talk about in terms of subphenotypes of autism. That's it.

Dr. Koroshetz: In terms of the prevalence of regression, but has anybody done kind of – instead of a meta-analysis – has anybody done kind of a detailed large number look at these kids as the regression's are occurring? Getting data on that? I think wasn't Sue Swedo trying to do that in intramural?

Dr. Insel: Yes, she was. I don't think she's ever published anything from that, or if she has, I haven't seen it.

Dr. Amaral: I don't think so. Yes.

Dr. Insel: But it might be worth checking in with her to see if there's something that's in press or something that could be cited. I know that is probably the

most detailed look where they've identified – I think it was over 100 children with a history of regression. And they've gone in to look very carefully at mapping it and trying to understand what the trigger might have been.

Dr. Amaral: Yes, I think Carlos was collaborating on that.

Dr. Pardo-Villamizar: Yes, yes. We are doing the immunological part. And I probably – I think that probably is important to clarify with Sue and Audrey. My understanding is that they may have already a paper in press about the issue of regression because I don't think that in the study there was clear evidence that the regression as a subtype was part of a continuum.

Dr. Insel: Right, that's my understanding, too. So maybe somebody can follow up with Sue and see what's the status of that. It would be great to be able to reference that here if it's in press, even if it isn't out yet.

Dr. Koroshetz: Even if you – in terms of a macrocephaly for the Courchesne study, is it clear what subtype – is it clear what subtype they got in that study? Were they just looking at sibs of –

Dr. Amaral: That study is a post mortem study of younger individuals. You're talking about the neuron count study, right?

Dr. Koroshetz: Right.

Dr. Amaral: The one I was talking about was – yes, it was seven post mortem brains and compared the number of neurons in the frontal lobe, or regions of the frontal lobe to age-matched controls. And that so you know the

Dr. Koroshetz: And then wasn't there an MRI study that showed that the macrocephaly was time dependent, like depended on when you looked at it?

Dr. Amaral: Yes. And that was the point of this new paper – is that it was actually looking at young enough cases. And so the take-home message from that *JAMA* paper was

that there were more neurons. But then there was a second – I mean you raise an interesting issue. You know, if the number of – if the percentage of individuals that have macrocephaly in autism is, you know – say it's 10 percent or 20 percent based on MRI studies – then if you look at seven brains post mortem then you'd predict only one or maybe two unless the statistics went in your favor would have macrocephaly or would have the enhanced number or precocious growth. But in that study, it was a very substantial number of the cases that had more neurons.

But the point is that when a replication study was actually tried and this is the Jacot-Descombes study. While there was an indication that the neurons in the frontal lobe might be a little bit smaller, there wasn't any difference in the total number of neurons. So I think at this point, with one saying there's more and one saying there isn't, we don't have an answer yet. We need to have more –

Dr. Koroshetz: But Tom, for the purposes of the report, from reading in the past, the advances were kind of – kind of clean. So here's something that's new. We could get into something where we could start a fight.

Dr. Insel: Well, I think you want to keep a high bar. I mean, the idea for an update is to talk about the small number of really transformative findings. And I would imagine that in some parts of the Strategic Plan there would be nothing to report. I'd be surprised if there was anything that was a transformative discovery in several of the questions.

On this one, actually I think there's quite a bit to talk about – but for this particular question. And David, this is a hard one. Can you just clarify the replication study? Was that done on the same brains or on different tissue?

Dr. Amaral: It was different tissue.

Dr. Insel: From different people?

Dr. Amaral: Yes.

Dr. Insel: And what do you make of this? I mean how do you think about this?

Dr. Amaral: So, your point is well taken, Tom. I don't think we have clarification at this point in time. So if it is the case that really what we want to do is present advances here as a new piece of knowledge that we feel confident in, my take on it would be we don't feel confident in this at this point in time. So I'm happy to postpone saying anything about this until we do.

Dr. Insel: And maybe this – again, we had talked about this on the immune side, putting something into a gap area where – and maybe that's the way to talk about this is to say that there's conflicting data about the hypercellularity or neuronal overgrowth, whatever you want to call it. And this is a gap area that we need to know much more about.

Dr. Amaral: Yes, I agree with that.

Dr. Koroshetz: Yes, that's good. Okay,

great. All right, so – I haven't heard Dennis or Kevin get on yet.

Dennis had just a couple of short items that he submitted. In terms of ASD and concurrent epilepsy, he talked about the – a mutation finding of a ketoacid dehydrogenase kinase, protocadherin. Talked a little bit about the trial that's going on in neonates with a GABA agonist because of the kind of different membrane potential for chloride in the neonate to block seizures and mentioned that it's being used in a study by Ben-Ari for ASD as well as neonatal seizures.

He also talked about a study that looked at the overlap of ASD and GI disturbances by Mazurek – of 2,973 children in the Autism Treatment Network, 24 percent had one or more chronic GI problems.

And those were basically – so it's quite short. Those were the major items he threw out.

Anybody have any additions or subtractions? Okay. Yes, that one I think was pretty

straightforward.

Dr. Insel: This is Tom. The only comment I would have here is this was to respond to what ultimately became of one of the objectives in the Plan about underlying biological mechanisms of co-occurring conditions with autism, including seizures, epilepsy, sleep disorders, wandering, elopement behavior in familial autoimmune disorders. So if there's anything really profound in those other areas – like on the sleep disorder side as well as the epilepsy side – this could be a good place to note it.

I think that the *Science* paper that came out a month ago on the BCKD-kinase finding is certainly important enough that it should be recognized here in the update.

Is there anything in terms of sleep that the or in terms of familiar autoimmune disorders or even the elopement and wandering piece in terms of biology that ought to be here as well?

Dr. Pardo-Villamizar: I don't think that

in the autoimmunity there is anything outstanding there.

Dr. Insel: Okay. And what about on sleep, anybody know? There's a lot – there's actually been quite a bit of interest in this. I know there's the Ashura Buckley piece that was published I think in 2011 and looked at the huge changes in sleep architecture in children with autism. I wonder if we haven't recognized that before; maybe that deserves to be cited as well.

Dr. Koroshetz: Okay, we can go after the sleep. I'm not sure Dennis – Dennis didn't come up with anything there, but we can double-check into that.

Dr. Insel: Okay.

Dr. Elizabeth Baden: This is Elizabeth from the Office of Autism Research Coordination. And I know that Beth Malow is working with the Question 4 group, and she's done a number of sleep studies. She might be aware of some of the most important biological findings as well –

Dr. Koroshetz: Yes, that is a good point.

Dr. Baden: I don’t know if someone might want to reach out to her or get her input on the day of the workshop as well.

Dr. Koroshetz: Yes, that’s her area of interest, so I’m sure she would have that nailed.

Dr. Insel: Okay.

Dr. Koroshetz: Okay, great. Now, Kevin unfortunately isn’t here, so he did a fairly extensive look at – so in terms of neurocircuits, he talked about some papers on disruption in synchronized activity across circuits for social information and processing.

He brought up the same paper I had talked about before looking at the MET variant as a potential modulator of key social brain circuitry. That was a study looking at MET risk genotypes in controls and autistic individuals. They found that the genotype predicted response to social stimuli

in both groups but more so in those with autism.

He mentioned the eye tracking studies. Elsabbagh revealed using EEG responses to eye gaze found that eye gaze shifts during the first year predicted clinical outcomes at 36 months despite similar patterns of gaze as measured by just the tracking alone. It was the brain responses to eye gaze in the first year as measured I guess with EEG synchronization.

In terms of sex differences, he talked about a paper by Dworzynski, finding I think a disparity that the diagnosis is less common in women and girls if they don’t have intellectual behavioral problems. I guess the implication there was that the boys may have the diagnosis made more easily without intellectual problems whereas girls would not.

And then he talked about the CNV study from Simons showing that females with ASD showed a higher frequency of new mutations

compared to males. Wait, did I get that wrong?

[Pause]

Dr.Koroshetz: I have to look into – he writes that females with ASD show a higher frequency of new mutation – 11.7 compared with 7.4 in males – as well as reliably higher numbers of new mutations – 15.5 compared to 2 with males.

Okay. The gap areas he put out were further studies on females with ASD – look at genes, brains, and behavior and lack of longitudinal studies of brain function. Need for longitudinal studies. And he brought up the Nordahl paper identifying an increased rate of amygdala growth in very young children with ASD as an example of the kind of things that need to be done more.

That’s my look at Kevin’s. Does anybody have any comments there? We’ll probably get back to him in terms of shortening this. But anybody have any ideas on things that should have been included here?

Dr. Amaral: The only thing that – not on that section but are you going to talk about the pluripotent stem cell section?

Dr. Koroshetz: Yes, we'll go to that next. Anything on the circuitry or the gender? Okay.

So yes – so the IPS cells. So Kevin and Alison I think had that. Alison's not on the call. We don't have a response from Alison.

Kevin in his email said that he wasn't sure if it was worth bringing it up. He talked about the paper on the Timothy syndrome, and then there was one other one he brought up. I can't remember it offhand.

But looking at the Timothy syndrome paper – that seemed to be pretty interesting to me.

Dr. Amaral: I was going to say that I thought that one should be highlighted as well. So there are two Timothy syndrome papers – one on heart and one on neurons, using neurons. The one on neurons, of course. But I mean, as signaling a new direction, I

think that that's an adequate paper to do that.

Dr. Insel: Yes, I would strongly agree – and not only for the biology but also for screening for novel therapeutics. They do that in the Pasca paper, in the Timothy paper where they show that they can use this to rescue the phenotype with a treatment in a dish. Pretty cool.

Dr. Amaral: Yes.

Dr. Koroshetz: Okay, yes. We'll mention in the email to Kevin that we discussed that in the call. But, I think that would be good. So we can add that in.

Okay, that's Question 2. We have 2 minutes left. I think what we're going to do on our end is try to compile these and then – not to make people upset but – we're probably going to have to start cutting some things. So clearly we want to be sensitive – if people we overcut – to let us know. But we have this word limit of 1,200, is that right? Yes. So that's what we're shooting for.

I think the next step for us will be to try to compile and shrink down, try and get close to the word limit. We may have to do a couple of iterations to get down there.

Dr. Insel: So Walter, can I just make three quick comments about this process?

The first is I thought it was very helpful in the section that David Amaral did where he started off by saying in the past year there had been over 225 publications. Just to give the audience a sense of the amount of activity in the area.

Remember, the original charge was a series of objectives that said things like support of these three projects to do X or support of these four projects to do Y. So when you can say that there are over 200 publications, it gives a sense of the vitality of the field. That’s great. And we should try to do that wherever we can.

The second comment is that, again, to keep a really high bar on the projects that we cite. There were a couple of things that

we didn’t cite here, which aren’t specific to autism, but I think are enormously important – like the project last year by Sestan and others on the developmental map of human brain transcriptional patterns, looking for the first time at how the human brain is developing over time, especially over fetal time at the molecular level. So even though autism isn’t necessarily mentioned there, that is the fundamental science that we need to make sense of all this other stuff. So it might be good to work that in at some point in talking about the molecular basis.

And the third comment: As you guys kind of consolidate this and figure out what the final very brief update’s going to look like, I want you also just to scan through the actual objectives. We’ve been doing this with a focus on where we started, which was what do we know and what do we need, that section of the Strategic Plan.

But when this ultimately gets published, there will be people who will cross-reference

whatever you write up in terms of the update with the objectives that were laid out in either 2009 or 2010. They'll be asking the question, have we delivered on these very specifically?

And so sometimes, it's just a matter of – where we really have delivered – it's just a matter of pointing that out in some way. That's why I mentioned that, in addition to seizures, we ought to be looking at sleep and autoimmune and other parts of this because that's what was called for in the original objective as Objective E.

But go through the list as you're writing this up and just be mindful that that is a question that every one of us should be asking of ourselves on the Committee. And the public has every right to ask of the IACC and of the scientific community, how have you responded to the objectives? So we want to make sure that we include language – whenever that's possible – that shows that we're fulfilling the charge that was given to us in

2009 or ‘10.

Dr. Koroshetz: Okay, makes sense. Which one is Beth on?

Dr. Baden: Four – Question 4 – treatments and interventions.

Dr. Koroshetz: Yes. So in terms of the subgroups, how ours was related to the kind of subgroups of people with ASD – helping to understand the etiology of the symptoms. We’re pretty – I think for the immunology – I think we have some really good stuff.

Dr. Insel: Well, you know, I can’t remember who said it, but on the question of regression, you know, the original charge was launch two studies that focus on regression. Actually, it’s prospective characterization. But if someone has now done a meta-analysis on 50 or whatever it was, some huge number – those kinds of things are just worth putting into context so that the public can see what is going on here on the very questions that we put into the Strategic Plan.

Dr. Koroshetz: Yes. Okay, yes. So we can

– that would be great – so, linking it up to the objectives.

Dr. Insel: Yes, I don’t think you have to word for word. We didn’t set this up in a way that we were going to do it point by point. But when it’s ultimately published, people will want to look at using the update to say how have we done.

Dr. Koroshetz: Okay. Yes, I think that’s easy to do as long as we pay attention to it. So thanks for that.

Dr. Insel: Okay.

Dr. Koroshetz: Any further comments? So Kate’s my assistant. She’s asking whether people want to incorporate changes and send them back to us or would you rather us take a shot at it and send it back to you.

Dr. Insel: Who’s going on vacation, Walter?

Dr. Koroshetz: Kate.

(Laughter)

Dr. Pardo-Villamizar: I may include some additional sentence on the immunology part

just to clarify the issues that Tom mentioned before and perhaps the Geschwind paper.

Dr. Koroshetz: Okay. All right, great. So yes, so if people want to send in comments in a short period, please do so, and then we'll get to work.

So for the face-to-face, meeting I think we'll have a good product. And will we work out the details at the meeting, Thomas, or do you want the product to be final or close to final at the time of the meeting?

Dr. Insel: Gemma?

Ms. Weiblinger: I think the purpose of the workshop is to have discussions and to make a final determination about what you want to include in the update. And then we'll spend the month of November trying to put it together into one discrete, hopefully kind of equal-in – parts document and then send it out again.

And the Subcommittee will meet formally again to formally vote on it. I think it's November 26th, isn't it? Yes.

Dr. Koroshetz: So we could have a long version, which has pretty much everything that people wanted, and then we can have suggestion of a shorter version that could be close to the final that goes in. But the longer one would allow the discussion to be wide open at the meeting. Would that make sense?

Dr. Insel: Well, but Walter, it might be easier if – because one of the issues that will come up then is what we cut out afterward. It would probably be better for the Committee, the workgroup on the 30th to see what you intend to put into the update.

So if it's much shorter than, for instance, what we talked about in the last hour, they should know that. And if they have concerns about pieces being left out, then we can hear it from them.

Dr. Koroshetz: Okay.

Dr. Amaral: Walter, this is David. I would second that. I think probably it would be helpful if your team put together

something close to the 1,200 word summary that you think you would like to submit and circulate that a little bit so that we can debate the balance of that 1,200 words.

And then after that process, that iterative process, we could then have something that we all feel reasonably comfortable with going into the discussion on the 30th.

Dr. Koroshetz: Okay; that makes sense.

Ms. Kate Saylor: And we submit our draft on the 22nd.

Ms. Weiblinger: Yes. Yes, to OARC.

Dr. Koroshetz: Okay. All right, sounds good. Thanks. Thanks, everybody, for your hard work, and we'll start circulating drafts.

Dr. Insel: Okay, Walter; have a good break, good vacation. We'll see you when you get back.

Dr. Koroshetz: Sure thing. Thanks everyone.

(Whereupon, the Question 2 Planning

Group call ended at 1:25 p.m.)