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INTERAGENCY AUTISM COORDINATING COMMITTEE

SUBCOMMITTEE FOR
BASIC AND TRANSLATIONAL RESEARCH

STRATEGIC PLANNING QUESTION 3 PLANNING GROUP

CONFERENCE CALL

TUESDAY, NOVEMBER 12, 2013

The Strategic Plan Question 3 Planning Group convene a conference call at 10:00 a.m., Susan Daniels, Executive Secretary, IACC, presiding.

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TABLE OF CONTENTS

PROCEEDINGS:

Operator: Welcome, and thank you for standing by. At this time, participants' lines are in a listen-only mode. This conference is being recorded. If you have any objections, you may disconnect at this time.

I would now to turn the meeting over to Dr. Susan Daniels. You may begin.

Dr. Susan Daniels: Good morning, everyone. Welcome to our listeners on the phone, to the IACC members, and to our invited participants on today's call of the IACC Strategic Plan Update Question 3 Planning Group.

Thanks for being here. We appreciate having you. Today we're going to be going over a couple of materials that are on the Web site. So for anyone who is listening, if you go to our Web site on the Meetings and Events page, you can go to the Materials link for this call and you will find both of the tables that the IACC members have. And you can access those materials.

Before we get started, I'd like to go through a roll call so that you know who's on the phone.

And the bios of all our invited participants will be posted this week so that those who aren't familiar with them can know who they are. Let's go through the roll call.

Lyn Redwood, are you here?

Ms. Lyn Redwood: here.

Dr. Susan Daniels: Thanks.

Cindy Lawler for Linda Birnbaum? Cindy, are you here?

Dr. Cindy Lawler: Yes, I'm here.

Dr. Susan Daniels: Matt Carey?

Dr. Matthew Carey: Yes.

Dr. Susan Daniels: Thank you.

Dani Fallin? And now I'm going through external participants, now at this time.

Craig Newschaffer?

Mr. Craig Newschaffer: Here.

Dr. Susan Daniels: Thanks.

Julie Daniels?

Ms. Julie Daniels: Here.

Dr. Susan Daniels: Thank you.

Irva Hertz-Picciotto?

Dr. Irva Hertz-Picciotto: Here.

Dr. Susan Daniels: And Joe Buxbaum?

Dr. Joseph Buxbaum: I am here.

Dr. Susan Daniels: Thank you. Well, it's great to have you here. On the previous call of this Planning Group -- well, to back up a little bit, we are in the process of working on the Strategic Plan Update for this year. And the IACC decided that this year they would like to do an evaluation of progress on the Strategic Plan as it's written. The Strategic Plan has been in place now for 5 years, and they wanted to get a sense of what has been accomplished.

And last time on our phone call, with just the IACC members in this Planning Group, they looked at the progress in terms of funding. And so we looked at one of the items that you have in your packets, which is the Cumulative Funding Charts. And we went over what they felt the progress had been in terms of funding projects that were listed as objectives in the IACC Strategic Plan. And so we got a sense of that.

And on this call today, we're asking our invited participants, in particular, to help us

think about what the progress has been in terms of what's been accomplished in the field and whether these types of targets, these types of objectives are on target, if they're being met, if they're still relevant, if there are particular barriers in the field that need to be addressed. And so we'll be looking to your expertise to help us with that.

So I have a table prepared for you that is called the Conclusions table, if you look at that in the materials that I sent you. And we're going to go over each of the 15 objectives in this question of the Strategic Plan. And we'll briefly summarize what was discussed from the last call.

And then we'll be asking for some input from all of you about how we think this area is progressing in terms of the science or in terms of other advances that may have been made in the field, and what are the specific issues that still need to be addressed.

So are there any other questions before we get started?

[Pause]

Dr. Susan Daniels: All right. So let's look at the first one. This is Objective 3, short-term A, 3.S.A: "Coordinate and implement the inclusion of approximately 20,000 subjects for genome-wide association studies, as well as a sample of 1,200 for sequencing studies to examine more than 50 candidate genes by 2011. Studies should investigate factors contributing to phenotypic variation across individuals who share an identified genetic variant and stratify subjects according to behavioral, cognitive, and clinical features."

And so the last time the Planning Group discussed this, they felt that the recommended budget has been partially met, at about $38 million, and this is based on the projects that were funded over the past 5 years by all funders, not just government funders, but also by private funders who are working in this field.

Progress had been made on this objective, and several GWASs and sequencing projects have been funded. But they felt that more information was needed to determine the specific targets of 20,000

subjects for GWASs and 1,200 for sequencing studies to examine more than 50 genes has been accomplished.

And we'd invite any of you to make comments on what you think of how this objective may be doing in terms of progress in the field.

Dr. Buxbaum: This is Joseph Buxbaum. So it's just a couple of points. I mean, 20,000 for GWASs is a good number because we know that, for example, in other complex disorders when you get to 20 to 25, you begin to find many real findings.

The autism world right now is stuck at about 6,000 unrelated individuals in the GWASs pool. All that data has been put together through the PGC, the Psycho-Genetics Consortium that we all, I think -- we are falling short of that 20,000 number.

On the flip side, with regard to sequencing, and if you -- you know, it's a little bit ambiguous here whether that means whole exome, whole genome, or targeted resequencing. But in terms of sequencing, there's been a lot of activity. And between the various funding

agencies, including the NIH and Simons and a couple of other ones, I think we can safely say that there are well more than 1,200 cases that have been sequenced on the whole-exome level.

And I think the hope is that there is sufficient resources already allocated that, you know, within the next 12 months we can get up to as many as, you know, 5,000 or 6,000 probands sequenced, together with the appropriate controls. So I think we're doing better there.

And in terms of number of genes, I mean, these first sequencing studies have identified somewhere, I would say, between 7 to 10, depending on how you count. And we do think that with existing infrastructure and resources, we might be able to get to a number that may approach 50, but may not.

Dr. Susan Daniels: Okay. That's helpful.

Dr. Buxbaum: I guess the final thing about genotype/phenotype, in other words, what's in blue on the left, you know, there are not a lot of studies except for the ones, for example, if you think about fragile X syndrome or Rett syndrome --

putting those aside, there are not yet a lot of funded studies that are taking a genotype-first approach, whether individuals are being ascertained by genetic variation, and then looked at in terms of phenotype.

And that's just not -- it's just not out there yet. Except, I mean, the Simons Foundation has supported something in 16 -- in one genetic lesion. And stratifying in advance by behavior of cognitive and clinical features has been tried; it hasn't been, to date, terribly fruitful. But that -- you know, I think that needs to be kind of pursued further. I'll stop there.

Dr. Susan Daniels: Great. Thank you. Does anyone else have comments on that area?

[Pause]

Dr. Susan Daniels: Well, that's a very helpful observation.

Dr. Hertz-Picciotto: Well, actually…Sorry. It took me a minute to get off mute. This is Irva. I just had a question, which is, does this aim -- would you say that this encompasses the copy number variant field? Or you know sequencing of

deletions and duplications and that sort of thing?

Dr. Susan Daniels: The way it was written wasn't terribly specific. So it could be interpreted in a number of different ways. Do you have particular comments on that area?

Dr. Hertz-Picciotto: I mean, you know, not really. I just -- I was just wondering whether to include that because, clearly, that's sort of an area that the last few years has really emerged as a major one. And, you know, I know there -- I can't say that I could summarize that literature myself. But I just -- I wondered whether 7 to 10 genes is on the low side in terms of what's generally been identified in the copy number variance yield.

It seems like there's more, but that's not my area. So I really can't speak to that.

Dr. Buxbaum: That's a great point. I think one thing that's kind of been nice to see is that chromosome micro-array is transitioning, in the States, at least, as the first-line kind of assessment of people presenting unexplained intellectual disability or autism.

And so there are now publications where they're taking CNV calls from these clinical micro-arrays in the tune of, you know, 15,000 independent subjects. And like you pointed out, they're making a lot of recurrent discoveries that are well more than 5 to 7.

CNVs, of course, often encompass many, many genes. And so it's hard to reduce a CNV to a gene. The 5 to 7 number I gave you was new genes had to discover, bodies, new methodologies of exome sequencing. CNVs are very important, and that's probably one area to think about ascertaining by recurrent variation and looking at phenotype, as has been done, as you know, Irva, for 22q11, for example, VCFS.

So I think that there is -- I think CNVs could be included here. There is a transition to clinical -- clinical bay samples. And one could ascertain individuals with a known CNV that are identified very early in life and do kind of natural history studies because so many are recurrent.

[Pause]

Dr. Susan Daniels: Great. Does anyone else have any comments here?

Dr. Newschaffer: This is Craig. I had another question, probably for Joe, in relation to what the thinking is in the field about the fruitfulness of investigations using quantitative ASD-related phenotypes as opposed to qualitative state for this type of research and whether or not there's been any progress and, you know, what the thinking is about pursuing this moving forward.

Dr. Buxbaum: So, you know, people have been trying it. And there hasn't -- nothing really has fallen out so obviously. There is some sense in the field, and it's controversial, that the presence or absence of intellectual stability will present with different constellations of genetic variation.

As I say, that's controversial. That's one quantitative measure that's being used maybe to some effect.

Some of the other ones, you know, really haven't, to my mind, gone that far. I think what would be interesting, Craig, would be to -- you

know, when you do look at the logically defined subtypes, whether it's genetic or otherwise, and you know, you begin to see that they look -- the gestalt is different or there are measures that are clearly different in those subtypes.

And I think that's probably a fruitful direction because, you know, that would begin to tell you how these subtypes split apart, on what domain, and maybe that can be applied. Those measures could be applied broader to see if you can't capture subtypes. But beyond that, I don't have any good ideas.

Ms. Redwood: Joe, I have another question. This is Lyn. You mentioned about working at the natural history of CNV. And I was just curious whether or not you felt it might be fruitful to look at those over time. My understanding is that some of these CNVs are acquired. So if you had, say, genetic, you know, material from birth that you could analyze and then look at later on, maybe 1 year or 2 years, or maybe even during the period of regression when you are following these high-risk siblings, whether or not that might yield

some useful information in terms of when these CNVs might actually occur and what might be triggering them.

Dr. Buxbaum: So I don't know of examples where, I mean, certainly, there are somatic mutations that occur. But the CNVs that people have been identifying to date in autism are germlines, so they happen at -- you know, whatever. They're either inherited, or they're de novo at the formation of the egg or sperm.

I mean, but it's also true that you could have a mutation, you know, at conception. But you'll still have regression at age 5. I mean, Rett syndrome is the classic example, right? The mutation is effectively, you know, doesn't seem to be a problem for the first 3 or 4 years of life. And then you begin to get this very profound regressive onset disorder.

So I think life history, one of the advantages of, you know, if you have kind of an individual at high risk for whatever reason because there is some molecular change, there's an environmental risk factor, there's a sibling, life history

allows you to, first of all, identify the early predictors, so you can think about early intervention. But it also allows you to think about things that we don't usually think about in autism.

I think we're discovering, for example, that, you know, a certain proportion of these recurrent molecular findings are associated with various kinds of regression; Rett syndrome is just one. But there is a cluster of mutations that seem to have a high risk of regression at late adolescence and profound regression. And that's something that the autism community doesn't think about so much, but the medical genetics people do.

And when you discover that these autism kids have the same lesion that the medical geneticists knew about already, you have to start thinking about, you know, what happens beyond autism? What are other things that we need to be aware of that are, you know, in the wings, so to speak, that are very, very, very dramatic and traumatic? And how do we get ahead of those?

I think life history, from an etiologically

driven perspective, is going to be really critical to translate the research findings into clinical findings of a meaning to individuals with the disorder.

Dr. Susan Daniels: Anything else before we move on to the next? This has been a great discussion.

Alright, so let's move on to 3.S.B: "Within the highest priority categories of exposures for ASD, identify and standardize at least three measures for identifying markers of environmental exposure in biospecimens by 2011."

The Committee members who looked at it last time determined that this recommended budget is only partially met and that there's been progress on understanding on the exposures, but more work needs to be done to apply this directly to autism research. And that progress has been made through projects funded by NIEHS, but those projects aren't captured here because they are not specific to autism.

So what do we think about the progress in this field? And what's going on here? What's happened,

and what kinds of barriers may there be to advancing this area further?

Dr. Buxbaum: I think we'd all agree it's underfunded. I would say there are some grants that I would maybe put in this category. There are some epidemiological or genetic [Inaudible] grants that really are taking a look in large scale at exposures. I mean, there's an ACE grant, Autism Centers of Excellence, that is what's called a Minerva consortium, which is seven countries looking at risk factors for autism.

Now, of course, they cannot drill down to the same level of detail as some of the things going on at MIND or the California registries. But you know, if you want to know whether valproate, as rare as it is, really is a risk factor for autism using modern diagnostic criteria, have it following 20 million kids is the way to do it, right?

So I would say the funding is better than shown here, but that's just maybe a personal bias. But I can think of a couple of grants that are trying to merge genetics and epidemiology -- PAGES

is the other one -- that I would think fall into this. At the very least, they're very powerful tools for looking at those high-priority categories of exposure, where possible, and then, you know, asking important questions about them.

Dr. Susan Daniels: And that is an issue that continues to recur throughout the Strategic Plan, because the way we do the coding for these projects is, each project is coded to its best-fit objective. And so there are cases where these projects could have fit in more than one, but they got coded elsewhere. So take note of those projects. I'm sure that they're in the portfolio now if it's somewhere. So we'll note that for the Committee.

Dr. Hertz-Picciotto: This is Irva. I would want to comment on some of the media that it would be useful to really advance the science and the use of, for example, newborn blood spots, where getting biomarkers, that are in the relevant time periods for autism seems mostly doable in the large cohort studies. And of course, those are, you know, far and few between -- few and far

between.

And I think, you know, that would be an area where the -- you know, for newborn blood spots, that can help in situations where there are teenage control studies. And there are a number of states that do archive those assessments. And they are made available to researchers.

I think, you know, as we've used them, so far, we've mostly been able to look at metals and I know there are groups not naturally working on autism who are trying to drill down and see ways to identify some of the organics and, you know, at very low levels.

But I think it's an area where a lot more technological creativity could be of tremendous use to this field as well as, you know, other fields.

I think there are lots of opportunities, and I just say one example.

Ms. Redwood: Susan, in looking at this objective and thinking back when it was first developed, my understanding was that there was a gap area in terms of really having standardized

measures for, you know, identifying using biomolar exposures and biospecimens. So this is more geared toward developing tools that we could use to then assess these biological specimens for environmental contaminants. Is that correct?

Dr. Lawler: So, this is Cindy. I think there were issues related to development of better analytic tools and also dissemination of those and having those embedded within existing epidemiology studies in ways that would lend themselves to pooling efforts. So the standardization language in that objective, I think, relates to that piece as well.

So there were lots of objectives, you know, wrapped up into this one. And I think what Irva spoke of previously is the need to sort of push the technology to be able to, you know, more accurately measure a wider variety of potential exposures; using, you know, newborn blood spots is the example that she gave that's particularly helpful.

Dr. Julie Daniels: So dovetailing on that, I think that the development work, whether it be for

blood spots or other biomarkers that can get back to that gestational period is always what we're looking for. And it seems like it is wrapped into this, but could be potentially highlighted more than it is currently.

Dr. Newschaffer: Yes, this is Craig. I mean, I agree. I think that this is -- the way this is currently written, it first had me thinking about some of the efforts that I know Irva's group has underway around developing -- the idea of developing sort of standardized self-report measures of exposure that can be easily integrated in large-scale epidemiologic or even large-scale genomic studies to get some baseline self-report measures of classes of environmental exposures.

And I think that work is moving forward and is important. But the other area that, as Julie was saying, that is implied here, but isn't clearly stated because of the emphasis on, like, key identified exposure domains where we have some -- our priority now is that they might be important in autism.

I think there's also the need for -- I think

the autism field would benefit greatly from any advances in the broader field of exposomics, you know, the idea of trying to develop new technologies that can develop biomarkers of exposures, perhaps biomarkers of cumulative exposure so that, if you have a study involving a child at the age of diagnosis, there's the potential for having biomarkers of exposures dating back through their life, or similarly for mothers, dating back through pregnancy.

This is a very, you know, nascent field. But you know, there has been work around this using, for example, DNA methylation as one such potential type of biomarkers for exposure. There's other work going on looking at albumin protein adducts, et cetera.

You know, I think that this is a field really, really very much at its beginning, and it's very much upstream from applied autism research. But I do think that our field would benefit from, you know, any advances in more basic exposomics. And I would like to see the Plan sort of reflect that in some way as a priority for autism, moving forward.

Dr. Susan Daniels: Great. Other comments?

Dr. Hertz-Picciotto: This is Irva again. Is there another place for biomarkers that might be less specific to exposures, but may be more indicators of particular biological processes? Is that somewhere else in here? I was looking, and I --

Dr. Susan Daniels: Yes. It's in Question 1. There is an objective about biomarkers in Question 1 that's pretty broad.

Dr. Hertz-Picciotto: Oh. Okay.

Dr. Susan Daniels: Some of the biomarker studies are likely there.

Dr. Hertz-Picciotto: Okay. Because I'm thinking of, for example, biomarkers in, you know, placental [Inaudible comment]. Would those fall under what's in Question 1? Or is that more --

Dr. Susan Daniels: It may or may not.

Dr. Hertz-Picciotto: Okay.

Dr. Susan Daniels: I don't know the specifics right now. But if there were some studies -- is there a particular study you're talking about?

Dr. Hertz-Picciotto: Well, I think that's an

area that many, many of the people in this virtual room I think have been interested in. And you know, we'd published a paper on trophoblastic inclusions. But you know, again, that's just an example of, you know, a biomarker that is found in a specific exposure -- biomarker, it's more of a -- potentially it's illuminating mechanistic pathway.

Dr. Susan Daniels: Right. But the Question 1 Objective talks about -- that one is -- it does talk about some developmental biomarkers and early biomarkers, as well as biomarker related to treatment results or treatment response. So it was really fairly about etiology. It did talk about etiology in that one --

Dr. Hertz-Picciotto: Okay.

Dr. Susan Daniels: -- so it's possible that there might be some projects there that would be relevant here, and we can check on that.

Dr. Hertz-Picciotto: Okay. Thanks.

Dr. Lawler: So this is Cindy again. It sounds like, from what I've heard, the experts here are weighing in the idea that a primary obstacle may

be in the, you know, sort of underfunded or inadequate development of exposure biomarkers rather than there are good biomarkers available that, for whatever reason, there's an obstacle to applying those in autism studies. Is that an accurate assessment of what I've heard?

Dr. Hertz-Picciotto: Well, I agree. That would capture my assessment of the situation.

Dr. Buxbaum: I agree.

Dr. Julie Daniels: I agree.

Dr. Hertz-Picciotto: That helps.

Dr. Susan Daniels: Thanks, Cindy. That's helpful.

Ms. Redwood: I think that's also reflected in the ACE 113,000 funding levels today, which was, you know, quite under what we had as a recommended budget.

Dr. Susan Daniels: Great. Well, thank you. Any other comments before we move on to the next one?

Well, let's go to 3.S.C: "Initiate efforts to expand existing large case-control and other studies to enhance capabilities for targeted gene-environment research by 2011."

And in this one, the Committee had determined that the recommended budget was nearly met. Work still needs to continue on this objective, but is limited by the number of existing large studies that can be expanded.

Does anyone have comments about this objective, where we are with the science, possible barriers?

Dr. Julie Daniels: So this is Julie speaking. I think that there has been quite a bit of funds directed in this manner. But I think that with the evolving nature of these studies, I wouldn't say that more work is unnecessary. And I wouldn't necessarily consider this complete in that sense.

I think there's still a lot more opportunity to milk this thing, study infrastructures for better investigations of some of these things.

Dr. Susan Daniels: Can you talk a little bit more about the evolving nature of the area?

Dr. Julie Daniels: Well, I think that some of these studies are still ongoing and increasing in sample size and increasing in the amount of data that they're collecting. And I think that to just

conclude that a certain dollar amount has been placed on this to support some research would limit the potential for more research to be done off these existing infrastructures.

So I guess I just think that they are a really great resource. And rather than starting from scratch for new resources, I think we could continue to support some of these studies in a way that would be still cost efficient.

I wouldn't want to conclude that, because the dollar figure has been met, the work has been completed in that sense.

Dr. Buxbaum: I wouldn't want to conclude that the work can't go forward because of the limited number of existing large studies, because when you go down to 3.S.H and some of the grants associated with that, as we said before, there are some -- there are quite a few large-scale studies that are getting -- that are growing and could be, you know, tapped or further expanded for it to really think about the gene-environment on.

Dr. Julie Daniels: In addition to that, I mean, I think there's potential for pooling and

collaboration among some of these studies that hasn't been tapped yet and would require resources to do so.

Ms. Redwood: [Inaudible comment] but the problem is lack of funding to actually analyze and discuss these. And is that what I'm hearing?

Dr. Julie Daniels: Yeah.

Dr. Buxbaum: Well, I'm reading the text. And it says, "Initiate efforts to expand" -- to expand, right? So the target here is to take existing studies, and I think there are some out there that could be expanded.

And I think that we're saying two things. The budget has been met. It's still an important topic. But also, the implication here is that there's not much more to be done because we've tapped out the large-scale studies, and I just don't agree with that. I think they could be expanded, which of course, means resources.

Dr. Hertz-Picciotto: Well, I think expanding can be interpreted in several ways. There's expanding the number of studies. There's expanding the number of people in the studies. And then

there's expanding the actual research that can be done within those studies.

And that's really the point about utilizing the array of biospecimens that have been collected. I think we've barely got -- I think that's true of all of the studies that we've barely scratched the surface on that.

Dr. Julie Daniels: Yeah. That was the point I was trying to make, is there was a lot of resource put into creating the infrastructure for these studies. And it would be a shame to sort of move on. So we just need to continue to tap the existing work that's been done, developing new hypotheses from the existing data, and potentially expanding upon the assays that can be done in the biomarkers that are collected in those studies.

[Pause]

Dr. Susan Daniels: Anything else on this?

Dr. Hertz-Picciotto: I think the genome [Inaudible comment] interaction aspects, you know, we have barely gotten into as well.

Dr. Susan Daniels: All right. Great. Well, thank you. Let's move on to 3.S.D then: “Enhance

existing case-control studies to enroll racially and ethnically diverse populations affected by ASD by 2011."

For this one, the Committee thought that the recommended budget looked like it had not been met, although it's possible that there are studies that are coded elsewhere, such as in 3.L.B, that may also reflect some progress on this objective.

And some of you who are experts in this area may be aware of how much this is happening in the field. And we're not sure of whether some of this inclusion is happening without additional supplements.

So any comments about this?

Dr. Buxbaum: I don't think we do well in this arena. I think obviously there is an ACE targeting just this specific issue. And so that's in 3.L.B, I guess, looking at the grant associated with that.

But whether the budget is met or not, there's no question that we're doing a poor job. And I think that -- I think the budget has been met, perhaps, but the objective has not.

Dr. Susan Daniels: And the budget hasn't been met. It's way below.

Dr. Buxbaum: Oh actually has not been. Oh, I'm sorry. I was reading the one above it. I take it back. Okay. Underfunded and under successful. Maybe they're correlated.

[Laughter]

Dr. Hertz-Picciotto: It's been collated in some place on the issue of underrepresented groups in the autism -- I mean, in this case, I think we're talking about the environmental and genetic -- the risk factor side of the research.

Dr. Susan Daniels: What kind of -- I don't think that anything like that has been done. But what kind of collation would be helpful? Just pure numbers of people of various ethnic origins that are represented in all grants portfolios? Or in --

Dr. Hertz-Picciotto: Well, grant portfolios that pertain to, you know, at Question 3.

Dr. Susan Daniels: So I guess I'm asking, on a practical level, we have a lot of different funders. It's not just NIH. There are a lot of other funders as well, although I don't know for

this particular objective how many different funders are involved.

But it would require looking at each individual project and somebody actually analyzing that. So I'm sure that that's not been done to date.

Dr. Hertz-Picciotto: I mean, for NIH, there is the, you know, targeted racial/ethnicity table that goes with every -- and the projected, and then the reports, the actual enrolled that go with NIH grants.

And that, at least, could be put together. It would be interesting. You know, I don't know how diverse the SEED study is. But it's in many metropolitan areas that are themselves diverse in their racial and ethnic composition. The CHARGE Study is about one-third Hispanic. And at the other groups, it's probably 40 to 50 percent nonwhite.

And I don't -- you know, I don't know about -- and so in terms of the European cohort, I think they tend to be less heterogeneous.

So just I think it would be useful to at least

see what those numbers are.

Dr. Susan Daniels: So Cindy, can you comment on that? I know that that would be probably a fairly significant undertaking. Is this something that you think that the ACC would be able to do?

Dr. Lawler: Maybe. I mean, I'm just thinking of -- we could certainly bring it back to them for strategies for how to do that in an efficient way.

Dr. Susan Daniels: Okay. We can talk about it.

Dr. Lawler: But I mean, not by Friday.

Dr. Susan Daniels: Right. It's not -- and one of the questions I would have is, would those numbers -- would it be worth the effort? It would take probably a lot of effort for someone to do. But is your conclusion already that it's inadequate anyway? In which case, it doesn't matter what the numbers are. Or would those numbers actually tell you something that's actionable?

[Pause]

Because I don't know. I guess, what would you do with that information if you had it right in front of you right now?

Dr. Hertz-Picciotto: I'm not sure who you're directing that question to. Since I brought this up, I mean I mean, I think what I'm not clear on is to what extent the Strategic Plan influences, you know, the kinds of RFAs that go out and that obviously play a role in what gets the submitted and what gets funded.

So, and probably in the area of services and treatment, this is at least as big an issue, if not bigger, than the Question 3 domain. But I think data is never a bad thing in terms of, figuring out what that next step should be.

Dr. Susan Daniels: Okay. So Cindy, then maybe we'll bring this back to the ACC to ask if they might be able to look into that before the Committee's report. Do you think that that data will be important?

Dr. Julie Daniels: Can I ask a slight question of clarification on this? I mean, I think this is phrased as racially and ethnically diverse populations. And I'm trying to distinguish the intent to really look at race and ethnicity from a socioeconomic status and how that would be

important etiologically versus for services and treatment, which I think is covered under a different panel.

Dr. Susan Daniels: Right.

Dr. Julie Daniels: And I think maybe both questions are valid. But I guess I'm trying to figure out what we would do with that information. Because you know, I think, given the studies that we are doing, we are really attempting to get representative populations, and it's challenging.

But what we would glean from that, from biological inferences versus treatment, might be very differently important.

Dr. Susan Daniels: So for this question, we would stick to just studies that are about environmental factors. Or I guess it could be genetic factors as well. So risk factor studies, not all the other services studies and things like that. So –

Dr. Julie Daniels: Yeah. And so then, I guess I kind of think probably less race and ethnicity than socioeconomic covariance would be important to sort of capture, because it changes the

susceptibility to risk.

Dr. Susan Daniels: I think that while the objective doesn't exactly state it that way, and then to send people off to go do an analysis of this -- I'm not certain about that.

Dr. Julie Daniels: Okay.

Dr. Susan Daniels: Cindy, what do you think about that?

Any thoughts, Cindy?

Dr. Lawler: Well, I mean, I think for the purposes of our -- I'm here on Friday. I heard, you know, broad agreement that we certainly need to do more along these lines.

Whether having data would shape the kinds of recommendations, it may be more useful if we had data to allow to kind of track future progress. I don't have any insight in terms of the rationale behind this objective, whether it had more than etiologic bent. So I don't think I could comment on that.

But what I did hear clearly is we're not doing enough, and we need to do more. Data would be helpful. We can bring it back to the ACC to see

what [Inaudible comment] ways to get that data in the [Inaudible comment]. But that won't happen before Friday, but I don't think we need that before Friday.

Dr. Susan Daniels: Right. I agree. I think that we could ask the ACC to help figure out a way to be able to have some sort of baseline to track in this area.

And for the future, it sounds like maybe more clarification. If at some point the Committee is going to recommend further action in this area, they might want some clarity around what's meant by this. And so the socioeconomic aspect of this might be -- they might want to clarify that.

Dr. Julie Daniels: That might just be my bias, so I don't want to completely derail the direction that you all were going with that.

Dr. Buxbaum: And just a quick comment and I'd like to move on, Susan and Cindy. You know, from the broader perspective of children's environmental health, there's been sort of a long sort of tradition of focusing on underserved low-SES populations because of their tendency to have,

you know, higher or worse environmental exposure profiles to a range of, you know, general hazards.

And you know, I think that maybe in here somewhere is the idea that some work should be done either exploiting the cohorts or populations that have been recruited for other purposes -- to look at autism in those groups and/or that the autism research community might want to think about taking a similar focus in terms of designing studies on high-exposure, low-SES, underserved populations to see if there can be some -- you know, I want to use the word "exploitation," but I don't mean it in the negative connotation -- some way of gaining some extra knowledge by studying those higher exposed groups.

Dr. Julie Daniels: Thank you.

Ms. Redwood: This is Lyn. Just to provide a little background again, when the Strategic Plan was written, gosh, in 2008, Susan, we were trying to identify areas that we saw as gaps that needed more focus. So I think that's why it specifically had in there that racially and ethnically diverse populations, because we were already collecting a

lot of data on socioeconomic status. So that was sort of considered a gap.

And one of the things that Irva said I think is something that's sort of an overall goal that I specifically have, is wanting to know what extent this Strategic Plan has on RFAs and what gets funded and how much is actually being utilized. And that's a broader question of the [Inaudible comment] that I think we should be asking at some point, too, in terms of evaluating our effectiveness with this type of approach.

Dr. Susan Daniels: So that's a pretty NIH-centric question. And I think in some upcoming reports, we have lists of RFAs. But I'm not sure exactly how useful that is. If the Committee feels they want to examine lists of RFAs, we can ask the ACC to put together NIH's. But it might not be completely fair if we don't do that for every funder, because many other funders also put out initiatives that we don't want to ignore.

So that would be another entire effort, probably, to do that. So the Committee might want to talk about that on Friday if they think that's

something they want to do and whether they want to try to do that before December.

Ms. Redwood: It might just help us, Susan, in knowing whether or not is it that RFAs were put out or we did have RFAs, but, you know, they weren't adequate applications or something along that line to identify what some of the barriers might be in these objectives that are, you know, underfunded and not accomplished.

Dr. Susan Daniels: So just to be clear, with these objectives, the expectation wasn't that agencies were going to release specific RFAs for all 78 objectives. That wasn't really what happened.

Most agencies did have -- they looked at these objectives, and they considered them when they were doing initiatives. But a lot of the research that's funded -- in fact, the majority is investigator initiated. And so these objectives also help inform the community. So there's a balance of that.

But we do have -- there are lists of RFAs. But they haven't really been put together in a format

for the Committee to review at this point. And if it's needed, we should find that out on Friday.

Ms. Redwood: Right. I was just thinking, moving forward, if we continue to have gap areas, that maybe we should have some discussion about how to fill those gaps and whether or not agencies should put out specific RFAs.

Dr. Susan Daniels: Certainly, I think the gap area discussion is very important. And, hopefully, on each of these calls we've had people from various funding agencies around. And so if you feel that, you know, there's an area that, actually that was an initiative that went out that addressed it, please speak up and let us know.

Alright, so is it okay to move on the next one? 3.S.E: "Support at least two studies to determine if there are subpopulations that are more susceptible to environmental exposures, such immune challenges related to infections, vaccinations, or underlying autoimmune problems, by 2012."

And for this one, the Committee felt that the recommended budget had been partially met, and the

intended number of studies was greater than two.

So, but what do you feel is happening in the field here? Is this field advancing adequately? Are there areas that need more focus? Are there barriers in this area that need to be addressed?

[Pause]

Dr. Buxbaum: I know what silence means here. But --

Dr. Julie Daniels: Any thoughts, anyone?

[Pause]

Dr. Hertz-Picciotto: Well, I mean, I'll speak up very briefly in saying I think this kind of goes along with what was said about there may have been some work done in this area, but more needs to be done. And so, regardless of whether there's been a budgetary goal met or not -- I guess not here -- I do still consider this an area that requires more attention.

[Pause]

Dr. Buxbaum: But I think one of the issues with this is that, you know, it assumes that you have strong subgroups, right? Strong subpopulations. We don't -- you know, if we don't

have those kind of well-defined -- then it's hard to develop a study where you have your subgroup and you're testing whether it's more susceptible to a second hit.

Dr. Julie Daniels: Yeah. I understand what you're saying. I guess I'm thinking of some of the work that we're trying to do and the control studies that we have now by creating such subgroups, although imperfect, to try to get at this. And I'm not sure what the threshold of two studies would be. But I think it's probably more on the quality of the ability to subset and look at this that would be important.

Dr. Buxbaum: Yeah.

Dr. Lawler: Julie, can you say a little bit more about what studies you had in mind?

Dr. Julie Daniels: I mean, I know, in SEED and in CHARGE, we've collected a lot of information about maternal health such as autoimmune history and things like that. So we can kind of superficially get at those preexisting conditions that might make someone more susceptible.

You know, it's imperfect, and it's hard to

measure the environmental exposure that goes along with it. So you know, I still think that there's a lot of opportunity to do more. And we've so far relied a lot on health history data to get at that, medical records and self-report. But I suspect that there are biological markers that could be -- or maybe there are some of those that are already being done in CHARGE to help with that characterization of that susceptible subgroup.

Dr. Hertz-Picciotto: Yeah. I mean, in the TRENCH study, we had actually a lot of collaboration on our team, which immunologists who have just been characterizing both the children and the mothers. And I would say it's been truthful. It's not been highly [Cough] [Inaudible comment] -- I'm sorry. I'm on the train.

You know, it's produced a lot of information about immunologic aberrations in children and then also in the mothers, you know, with this paper and translation psychiatry on the maternal defense set of children whose mothers make antibodies within the brain tissue.

So there is work going on in this area. And

you know, exactly where it's going to lead it's not clear. But I think there's been some truthful investigation and that there's certainly room for a lot more.

[Pause]

Dr. Susan Daniels: Other comments?

[Pause]

Alright, hearing none, let's move on to 3.S.F: "Initiate studies on at least 10 environmental factors identified in the recommendations from the 2007 IOM report 'Autism and the Environment: Challenges and Opportunities for Research' as potential causes of ASD by 2012."

In this one, the recommended budget has not been met or has been partially met. And it appears that there has been a significant decrease in the number of studies to this objective. Further work in this area is needed.

How do you feel the field is progressing in this area? Or perhaps some of you have information that the Committee may not have had in front of them when they discussed this the last time? Any thoughts about this?

Dr. Julie Daniels: Is there anything from the lit review effort that would shed light on this?

Dr. Susan Daniels: Which lit review effort? There hasn't -- what the Committee looked at last time was, they really looked at what kinds of projects have been funded. And they found that there were not very many projects assigned to this objective, which doesn't necessarily mean that there might not be projects that were assigned to another objective that are related to this. But they didn't look at the literature [Inaudible comment].

Dr. Hertz-Picciotto: Is it possible to know which studies [Inaudible comment] and which of these sub aims?

Dr. Susan Daniels: Yes. So if you go to the Cumulative Funding Table that I provided, at least for 2008 through 2010, there are links to the projects. And so you can pull up the project list if it's 2008 to 2010.

I actually have separate project lists for 2011/12, and I didn't put them in your packets that I sent out to you because I didn't want to

overburden you with attachments and make it confusing. But we do have those lists, and there are in fact on the Web.

If you were to go to the Question 3 Planning Group meeting that happened at the end of September, it's listed as an attachment. They're called full project funding lists or something along those lines, for 2011 and 2012. And so we have a full list of all the projects that were assigned here, some level of detail about the PI, the institution, the amount of money, the title of the project, et cetera.

Dr. Buxbaum: I mean, I wasn't around for the last call.

Dr. Susan Daniels: Right. Not everyone on this call received those. But they are on our Web site. If you feel the need to look at it right away, it's there. And if you want, after this call, I could send that to you as a supplement. I just didn't want to overwhelm you with paper or documents before this call.

But we do have lists. And if you were to go to the Cumulative Funding Table that I sent you, at

least -- now, this is 3.S.F -- for that one, there are projects in 2008 through 2010. So 19 projects in 2008, 14 in 2009, 5 in 2010. So you could click on those links, and then you would pull up the projects.

And then for 2011/12, there were 3 projects and then 1 project. So that's the drop-off that's noted.

Dr. Buxbaum: So I don't know what the right time to ask this question is, whether it's 3.S.C, 3.S.F, or some other 3.L something.

But, you know, one of the things that, looking forward, the field can now do with a lot of robustness, is, you know, when there's an association between an environmental factor and any disorder, there's always a question about the direction of causality. Is it causal, reactive, or independent, right?

So you know, there are studies, for example, in western Australia, that say that low birth weight in autism is also found in unaffected siblings -- sorry, sort of perinatal events are also found in unaffected siblings of kids with

autism, suggesting that there's a family risk for something that can produce both, kind of perinatal events and autism, right? So that's a reactive model.

And I think now, since we are getting to the point of having some recurrently seen environmental associations, there are epidemiological and even, recently, genetic methodology to actually dissect out the direction of the association, right? Is it causal or reactive or independent?

And it's not only captured in any of these. I mean, you could say it's captured in all of them. But as a specific kind of way of bridging the findings and understanding, you know, what's the cause and what's the effect, I think that needs to be better formulated in some Strategic Plan.

Dr. Susan Daniels: So how would you state that?

Dr. Buxbaum: Understanding -- you know, for those reliable associations identified with autism, you know, more studies that set the direction of the association.

Dr. Susan Daniels: Okay.

Ms. Redwood: Was that Joe?

Dr. Buxbaum: Yes; that was Joe.

Ms. Redwood: Hey, Joe. Thanks so much, because that was actually the question I was going to ask, because we do have several studies especially looking at air pollutants and pesticides and metals that, when you denote what are the next steps to really determine, you know, if there are issues, say, you know, etiologic? Or how do we combine that with genetic risk factors?

So that's really important. And I think that will help us a lot in terms of identifying where we go next with the Strategic Plan. So that's really helpful.

[Several speakers]

Dr. Buxbaum: And that's "environmental" quote/unquote factors, like preterm birth or maternal medication use, which, you know, are actually more directly related to genetic risk. And you can actually measure the correlated genetic risk to two things in a family, right? You can say, is mom's medication use genetically

related to the kid's autism? Or is it that the medication caused the autism?" So there are really sophisticated things being applied in other disorders, which autism, I think, needs to catch up on.

And then, of course, as you said, the more traditional -- the way most people use the word "environmental," right, things outside. But even there, somebody sees a buildup of a certain, you know, heavy metal. It could be from exposure, or it could be kind of internal metabolic process, right?

Ms. Redwood: Right. And that really puts us to, you know, potential treatments and also prevention, which is where we ultimately want to be?

Dr. Buxbaum: Yeah.

Dr. Susan Daniels: Great. I think that that might be a topic that you want to bring up again at the workshop on Friday, as we'll be talking about future direction. But that's a great comment. Other comments from others?

Alright, so then, let's move on to 3.F.G:

"Convene a workshop that explores the usefulness of bioinformatic approaches to identify environmental risks for ASD by 2011."

And this workshop took place in 2011, sponsored by NIEHS. And we've provided the link to the workshop report that's posted on NIEHS's Web site.

So what do you think about this area in general? What's the status of the field, and what are the possible next steps, or barriers, or other things that you think need to be discussed for this objective?

Dr. Hertz-Picciotto: Well, it seems like the shield was somewhat in its infancy in terms of bioinformatic approaches to environmental risks. And Craig kind of alluded to this when he was talking about the exposure. And you know, I mean, there are, what a couple of people possibly worldwide here that seem to be working on, at that level.

So you know, I mean, I think we've hardly gotten anywhere on this. And the workshop did happen, and I thought was actually -- I think it

was, if I'm remembering the workshop, I think it was really [Inaudible] workshop. But the actual -- you know the next step. But that's not what this aim is.

In terms of this aim, I think it's good. But it's, again, only a beginning in terms of where things should be going [Inaudible comment].

[Pause]

Dr. Susan Daniels: Anything else on this one?

Dr. Newschaffer: Are there any concrete plans to follow up on the workshop? Or any action items that emerged from it? I didn't participate in that workshop.

Dr. Susan Daniels: Cindy, are you on the line?

Dr. Lawler: So I think we've tried to encourage the use of bioinformatics approaches and sort of biologically informed, you know, ways to integrate data across domains in our unsolicited portfolio. I mentioned on the last call, we had invited somebody to come talk to us about data visualization [Inaudible comment] at this workshop at the EEARN Epidemiology Network at INFAR.

This is an area that would be encouraged in

future initiatives that NIEHS is considering.

Dr. Buxbaum: Back to Craig's point. There's something -- there's some link between 3.S.B and 3.S.G in the sense that there is -- the field is in its infancy. And you know, there really is a role for a workshop on kind of reliable measures and standardized measures for identifying, you know, biomarkers.

One thing we're doing here is teeth. And it turns out you can do amazing things with teeth, right? And I think, you know, I think that there probably is a place in the nearest future to kind of think about the technology part of -- bring people's awareness about what can be done reliably so that they begin to implement it in their studies.

As they collect families, you know, why not collect some standardized assessment and/or biological material that can be used to reliably, confidently measure exposures?

[Pause]

Dr. Susan Daniels: Other comments?

Ms. Redwood: Susan, yeah, this is Lyn. I just

clicked on the document, and I don't think I have the right one that's linked. Because that actually goes to the meeting that was held in 2010 that [Inaudible] more broad looking at environmental factors. In this, it says that the workshop that correlated with this objective was held in 2011.

Dr. Susan Daniels: Okay. Well, we'll have to look at that. It's possible maybe I made an error in what I linked in.

Ms. Redwood: Yeah. I don't think that's the right one.

Dr. Susan Daniels: Okay. Sorry about that if I made an error. We'll look at it. And I know that Cindy sent me something. So we'll see if it's possible that I didn't get the right one.

Ms. Redwood: [Inaudible comment], and I don't think I attended that one. So that's why I [Inaudible comment] don't think that's the right one.

Dr. Susan Daniels: Okay. Thanks for letting -- sorry, what? Oh, okay.

So Cindy, is the report from this workshop posted at this point?

Dr. Lawler: I don't know if it's posted on our Web site. I can resend you.

Dr. Susan Daniels: Oh, you don't need to resend it to me.

Dr. Lawler: Okay --

[Several speakers]

Dr. Lawler: -- I'm pretty sure I sent you the right one.

Dr. Susan Daniels: Yes. You did send me something.

Dr. Lawler: Okay.

Dr. Susan Daniels: And maybe the discussion was whether it was going to get posted on your Web site. And I might have grabbed the wrong thing off our Web site. So I'll check on that, and I can send that out to the Group when we fix that. Okay. Thanks.

Let's move on to 3.S.H: "Support at least three studies of special populations or use existing databases to inform our understanding of environmental risk factors for ASD in pregnancy and the early postnatal period by 2012. Such studies could include:

Comparisons of populations differing in geography, gender, ethnic background, exposure history -- examples are prematurity, maternal infection, nutritional deficiencies, toxins -- and migration patterns; and Comparisons of phenotype, examples, cytokine profiles, in children with and without a history of autistic regression, adverse events following immunization, such as fever and seizures, and mitochondrial impairment. These studies may also include comparisons of phenotype between children with regressive ASD and their siblings; Emphasis on environmental factors that influence prenatal and early postnatal development is particularly of high priority. Epidemiological studies should pay special attention to include racially and ethnically diverse populations."

So that's one of our longest objectives in the Strategic Plan. The Committee felt that on the last call that the recommended budget had been partially met and that the funded projects covered many of the aspects called for fairly well. There were somewhere around 30 projects associated with this objective, and that, while progress is being

made, it needs to continue.

But do you have insights from the field in what's happening here? And what are the areas that are doing well? What are the new opportunities, barriers, other issues? What are your thoughts?

[Pause]

Dr. Newschaffer: This is Craig. I think the one area where work is moving forward is in relation to preterm cohorts. I think there are a couple of projects underway looking at that. I know there's one study in New Jersey. And I think I remember hearing of a few others.

But other studies with ASD endpoints focused in special populations, I really don't know too much that has gotten off the ground recently.

Dr. Hertz-Picciotto: Well, maybe the other part of it, because it's special populations or use [Inaudible comment].

Dr. Susan Daniels: Right.

[Inaudible comment]

Dr. Hertz-Picciotto: I think maybe that second part is where there has been the most work. I mean, certainly, there are [Inaudible] papers out

now about maternal infections, several about nutrition, toxins somebody mentioned. Air pollution, that's been a really kind of burgeoning area, I think partly because air pollution one doesn't have to go out and do the measurements yourself as an investigator. There are these large monitoring databases available, you know, in many areas.

So certainly there's been probably quite a bit of work. You know, not nearly enough, given the magnitude of the issue and the complexity in the ASD and the pathways and so forth. But I think the focus in pregnancy and the early postnatal period, you know, it has been actualized in the work that's been done.

Dr. Newschaffer: Well, I agree. Sorry, I was rereading the aim. I think the [Inaudible] existing databases have definitely been the dominant. But special populations I think, has lagged a little behind. And I guess the objective is agnostic as to which is the preferred approach.

But I definitely agree, and especially with the iCARE and Minerva projects now and the

Horizon. They're also capitalizing even further on existing databases. So there's definitely been great progress in that regard.

[Pause]

Dr. Susan Daniels: Any other comments on this one?

Alright, so let's move on then to 3.S.I: "Support at least two studies that examine potential differences in the microbiome of individuals with ASD versus comparison groups by 2012."

And the Committee concluded that the number of projects in this area has been projects -- with six projects in 2012 -- but that the projects appear to be very small projects, which suggests that they are possibly insufficient to really complete the intent of the objective. And the high cost of required technology could be one barrier to completion of this objective.

So what do you feel is going on in the area of microbiome research and autism? And what are the needs, the progress, the barriers in this field?

Dr. Newschaffer: Well, they are small studies,

no doubt. One of the things about the microbiome is that it does take not only a lot of technology, but that the number of experts, you know, who really can analyze the data well, it seems turnkey, but it's not, right?

That's both on -- there's just measuring the 16S and then there's measuring the broader diversity of organisms, and there's even measuring some of the gene products -- RNA, for example. And so I think the field of autism would be well -- would do well to actually make sure that there's -- that the experts who come from the microbiome field -- then, you know, pile the studies that are probably underpowered and possibly not using the newest kind of analytical technologies.

[Pause]

Dr. Buxbaum: I think it's an important area, in short. I think it needs to -- I think if somebody -- with any complex sort, if somebody walks in with, you know, 20 and 20, most people are going to be a little skeptical where autism is such a clinically and etiologically heterogeneous disorder, right?

So it probably needs either subgroups or large numbers, and it needs kind of a very thoughtful molecular analytical plan.

Dr. Susan Daniels: [Inaudible comment] about ways to approach that?

Dr. Buxbaum: Sorry. All I heard was a train horn or something in the background. I didn't hear the last question.

Dr. Susan Daniels: It was Susan. I was just asking whether you had any thoughts about ways that some of those limitations could be addressed. Would this be by launching entire new studies or building on maybe other efforts that are going on elsewhere that aren't currently specific to autism?

Dr. Buxbaum: Well, you know, I don't think of the microbiome as being any less complex than genetics or the environment -- environmental, right? So I think that it would be hard to be done on the cheap, and it would probably involve launching new studies but borrowing experts who don't work in autism but who have deep knowledge of those kinds of analytical and molecular

approaches.

Dr. Newschaffer: This is not my area. But is there also a hurdle in terms of sample availability here? I mean, if you're talking about intestinal microbiome, for example, which I know is only one microbiome, you know, you have to have the samples collected. And while it can be a little challenging, depending on the study design, the age of the study population, et cetera, it's not hugely difficult.

And you know, perhaps this is an area where if the samples were available, that would help catalyze some of the tougher work that needed to be done? I don't know.

Dr. Buxbaum: Yeah, absolutely. Yeah. It's not hard to collect certain microbiome samples. And stool is an easy one for young kids. You know, if you use a diaper, right? So I think you're right. If there were appropriate data repositories, if you will, some of these large studies can kind of begin to collect those, and it could be the basis for a larger effort.

Dr. Newschaffer: In our early study, and I

think also in Irva's MARBLES study, we've collected meconium samples. And we've been contacted by more than a couple of microbiome researchers. There's some controversy about whether or not meconium is a useful matrix for microbiome. Yes, in fact, it's sterile; is it not sterile, et cetera. So that's been a little bit of an impediment to things moving forward.

But I got a little bit of the sense that, if you build it, you know, if you build a repository of samples, then the microbiome people will sort of find you. And that might catalyze work in this area.

Dr. Hertz-Picciotto: Well, I would second that if I was -- and my train here is making noise. But I just wanted to add, before I go back on mute, that linking microbiome with metabolome, I think, is -- would be a good direction to go. It's extending outward.

Dr. Susan Daniels: Great. Are there other thoughts?

[Pause]

Good. Alright, so let's move on to 3.S.J:

"Support at least three studies that focus on the role of epigenetics in the etiology of ASD, including studies that include assays to measure DNA methylations and histone modifications and those exploring how exposures may act on maternal or paternal genomes via epigenetic mechanisms to alter expression, by 2012."

The recommended budget has been partially met, and there were a number of projects in this area -- 22 in 2012. And so on the last call, the Committee felt that the momentum in this area seems to be good, and it needs to be maintained.

But do you have other comments about the status of the science in this area, where the new opportunities, the needs, barriers, et cetera?

[Pause]

Dr. Buxbaum: I mean, I think it's correct that there's some action in this area, right? Looking at exposures, you know, and methylation, for example. I think and certainly the momentum should be maintained. There's no question there. And again, it goes back to the question of available samples, right, whether there are blood spots or

whether they are, you know, placenta, whether there are things. Where there are samples, you can get -- you know -- you can get a lot of interest from people who do this on a large scale.

Dr. Susan Daniels: And that's someplace where they may -- between this objective and the previous one, and some of the other ones that we've discussed -- there may be some overlap with the Question 7 people that are looking at research infrastructure. If there are needs for samples in certain areas, that will be something important to bring up at the workshop.

Dr. Hertz-Picciotto: The other work that's been going on is figuring out how to do epigenetics and, you know, very small samples, you know, like blood spots and small-volume types of media. So that work, I think, and the [Inaudible comment] between this and development of biomarker methods.

Dr. Lawler: This is Cindy. It's a question for Joe. I'm not sure. How much work is being done beyond methylation? I know there are a number of studies that have looked at methylation.

Dr. Buxbaum: What do you mean beyond methylation?

Dr. Lawler: I mean --

Dr. Buxbaum: The epigenetic marks?

Dr. Lawler: Right.

Dr. Buxbaum: So, there's a little bit -- I mean, I was going to say -- not much. I mean, people are looking at some of these other epigenetic signature and post mortem CNS tissue, which there's not much of, of course. But when you think about these kinds of marks in other samples, you know, if it's a blood spot that's been kept in a basement for 20 years, you know, probably a lot of those have gone away.

There are blood spot repositories, not in America that I know of, but in Europe where everything is frozen at minus-20 and there is interest in trying to look at things besides methylation in those samples. Right? Can you take a little bit of the dried blood and actually do something that's based on proteomics or something like that. And I think that, unfortunately, there's not a lot of material per blood spot. It's

going to be very constrained.

But you know, it could be done. And it certainly can be done with core blood or placental tissue. I just don't know a lot of people doing it.

Dr. Newschaffer: But I also think that, Cindy, it's a little -- it's sort of -- I mean, while there has been work done on DNA and autism, in a couple of sample sets, I mean, if you step back, take the larger view and compare it to genomic work, you know, the amount of work that's been done is miniscule.

And you know, it is equally complex, and there's need for replication. There are going to be problems with false positives. So to the extent that we think, you know, the epigenome holds some clues for autism etiology, you know, even DNA methylation, I think just because we've managed to fund a few studies, thinking that we should move on to different marks is a little [Inaudible comment].

But I just think that we need to do more also related to DNA, and I think the field is still at

its infancy.

Dr. Lawler: Right. No, I was getting more at some of the sample preservation issues that Joe mentioned.

Dr. Newschaffer: Got it. Got it.

Dr. Lawler: But sort of, my understanding is it's more difficult with, you know, other than methylation marks.

Dr. Hertz-Picciotto: Just to recall [Inaudible comment], Joe that the California specimen archives is frozen at minus 20. I think the issue is, how long before the specimens, between when it's collected and when it actually makes it into the freezers. But --

Dr. Buxbaum: As I was saying, and I said, wait. Isn't there one in America?

[Laughter]

Dr. Hertz-Picciotto: But I don't think California is alone, because I know of several states that were --

Dr. Buxbaum: I think there was one in the Midwest, too, right?

Dr. Hertz-Picciotto: And I think Oregon may

have established one. I remember being contacted by people from Oregon when they were working on their -- getting it started there. So anyway [Inaudible comment].

Dr. Buxbaum: Yeah.

Ms. Redwood: This is Lyn and I have a question for the scientists on the phone, being a nonscientist. If you could clarify a little bit for me with regard to these abnormalities detected and methylation. Is there some things that are amenable to treatment if they're identified? Because if that's the case, that's very promising. And I feel like it should be an area we should be focusing more on.

[Inaudible comment]

Ms. Redwood: Did anybody talk about that potential there, if we are to identify these patterns of DNA methylation abnormalities to start focusing some in the area of treatment?

Dr. Buxbaum: So in terms of, you know, in terms of things that regulate DNA-meth kind of methylation, they do exist, right? H-tac inhibitors, things they're using in cancer?

They're very nonspecific, right. So the question is, you know, are there just general epigenetic changes in certain subclasses of autism like Rett syndrome? The answer is probably yes. How would you target them with [Inaudible comment]? It would be tough.

I think if there are specific epigenetic changes that you might find, they really would kind of implicate a certain pathway in the same way that a gene might, right? So then you'd still have the work cut out for you to then take that finding into kind of a pathway that you could think about therapeutics. It probably wouldn't be specifically around methylation.

Now one of the nice things about methylation and one of the interests, I think, is that, you know, if there is an environmental exposure, it might be that methylation is the mediator. So that gives you a tool to kind of link an environmental phenomenon or association with a downstream kind of epigenetic change, and presumably, then, a downstream gene-expression change.

And so it gives you kind of -- it's a means of

kind of developing a kind of a causal pathway and reduces something that can be quite hard to capture, like, you know, if environmental factor x increases the risk for autism, you know, we know that alcohol is a bad thing and increases risk for FAS and things like that. But the exact mechanism of how that does it is opaque, right -- really unclear.

And so if there is a mediating variable like methylation, you might be able to take something like, you know, a broad -- an environmental factor that has lots of effects and reduce it to a specific -- a very manageable number of downstream effects that seem to be mediating variables.

So in that sense, you know, all this is around treatment. But I don't think it's an immediate -- it doesn't translate immediately to a therapeutic opportunity. Does that make sense?

Ms. Redwood: But my point was, you know, like where do we go next with this?

Dr. Hertz-Picciotto: Well, I think one of the interesting hypotheses right now related to methylation is this folic acid finding. Because we

know folic acid is a donor or a methyl donor. And it's not clear why it seems to have a protective effect. But one of the hypotheses would be that it's -- you know, a deficient -- and not necessarily deficient in the sense of what we think of as deficient -- but maybe a low [Inaudible comment] or low levels of folate because of genetic susceptibility --

[Background noise]

Dr. Hertz-Picciotto: I'm so sorry. I lost my chain here -- train of thought. Does the methylation -- that there are impairments because of genetic susceptibility, then some mothers may have lower folate levels. So the possibility that epigenetics might be a mechanism explaining these epidemiologic findings for protection when mothers took their prenatal supplements prior to conception, it really seems like a promising one, although it may be much more complex than simply the amount of mental groups available.

Effects certainly, I think, may have some kind of translation potential down the -- you know, maybe not far down the line, or maybe far down the

line.

Dr. Susan Daniels: Thank you. Any other comments for this one before we move on?

[Pause]

Great. Let's move on to 3.S.K: "Support two studies and a workshop that facilitate the development of vertebrate and invertebrate model systems for the exploration of environmental risks and their interaction with gender and genetic susceptibilities for ASD by 2012."

And with this one, the Committee members who met last time felt that the recommended budget had been partially met. And some projects have been funded, but it appears there's a downward trend. And that there may be some overlap with projects from 2.S.B. That's about projects on gender.

And there may have been a workshop held by NIEHS, but I wasn't able to look into that further, whether there was a workshop. I don't have any information about that.

Dr. Lawler: This is Cindy. We did not have a specific workshop that focused on this. It was one area that was covered in the 2010 workshop that

was, you know, broader. And it was really meant to sort of bring together scientists from other complex diseases to help us think about different kinds of approaches for addressing environmental risks.

Dr. Susan Daniels: Okay.

Dr. Lawler: Autism. And I think that was the workshop that Lyn -- that was probably one that you sent out by mistake.

Dr. Susan Daniels: Oh, okay. So I'll put that here. That's probably what happened.

Dr. Lawler: So that animal model was a section of that, but it was not by any means meant to be the focus of that workshop.

Dr. Susan Daniels: I see. So what do you feel about the status of this area, the development of model systems for studying environmental risks and gender and genetic susceptibilities?

[Pause]

Dr. Lawler: So this is Cindy again. I mean, I haven't -- I didn't pull up the specific projects. It's certainly greater than two. But I do know, from talking to investigators, these kinds of

studies have been hard to -- we have not funded as many as I would like.

[Several speakers]

Dr. Julie Daniels: Cindy, do you have a sense for -- sorry. Do you have a sense for the lack of funding because the appropriateness of the models is lacking or just because it hasn't happened?

Dr. Lawler: I think there's a mix. I think there's certainly always the immediate reaction of, you know, “You can't model autism in this organism.” So that there's part of that most people are more sophisticated that are developing proposals and are trying to model aspects of the phenotype. That said, there's -- you know, it's an area where there's not much out there and it's really, I think, difficult to sort of break in and gain some traction.

So the number of funded studies is pretty low and I don't think necessarily reflects the interest that, I think, I see and I, you know, hear about from people calling me with --

Dr. Hertz-Picciotto: It does seem as if these animal models have developed quite a ways over the

last few years. And I think Jackie Crawley is, you know, one of the believers in this area, but others as well. They haven't been acquired so much for looking at environmental risk factors.

And I think that there's -- this is again one of those areas where the opportunities are probably greater now than they were 3 or 5 years ago because these, you know, animal model systems that model aspects of the behavioral, you know, phenotypes, maybe not all together, but separately, you know, social interactions or [Inaudible comment] behaviors, and so forth.

But I think, you know, in some -- to some extent, there's now more interest that could support this work. But the use of those models has not focused on the environmental side. It's been more for understanding behaviors and possibly more on the treatment side.

[Pause]

Dr. Susan Daniels: Yes. And many of the studies for developing animal models, I believe are in Question 4. So I think that you're probably right that most of them don't talk specifically

about environmental risks, because if they had, they would have been coded to this objective. Anybody?

Dr. Buxbaum: Because it's very specific around environment and interaction with gender and genetics, you know, it's a different thing. And there are probably lots of new opportunities now because there are genetic models, you know, and other models. And you can -- the interaction question could be looked at.

Dr. Susan Daniels: Okay, good. If there aren't any other comments, let's move on to 3.L.A: "Conduct a multisite study of the subsequent pregnancies of 1,000 women with a child with ASD to assess the impact of environmental factors in a period most relevant to the progression of ASD by 2014."

And the Committee found that the recommended budget for this objective had been met, but that emphasis should continue in this area in the future. And the Group was concerned about the lack of continued funding for EARLI.

So are there any comments that you have about

this objective? What's the progress? What are the concerns, barriers, opportunities?

Dr. Buxbaum: I can chime in and express my concern for lack of funding for EARLI but that's parochial, I guess, on my part.

[Pause]

Dr. Newschaffer: It's certainly of ongoing importance. The, you know, the objective should be -- I think it was good the money went in, and I think the objective should continue. I think that -- I'm sure and it's disappointed EARLI as not funded. And some of the other studies, you know -- none of the studies were well funded to collect bile materials, to the best of my knowledge, right?

Dr. Buxbaum: Yeah, well, from the glass-half-full perspective, I mean, MARBLES is still funded and is continuing, which is another [Inaudible comment] pregnancy cohort study.

EARLI, though, we've had to stop enrollment about a quarter of the way toward our goal of 1,000 is trying to capitalize on the rich bile repository we have on that small number of

pregnancies and have had, you know, some success with some analytic grants to analyze what we have already collected and are continuing to write and try to do what we can with the small cohort that we have.

Dr. Julie Daniels: I'm just looking at this from sort of -- the funding has gone to support this, or some aspect of this. But I feel like this is such an important opportunity, you know, MARBLES and Early both, to really get the requisite biomarkers that we need at the right time. And, you know, with MARBLES, it just seems like enhancing that effort would be important if there are funds to shoot in that direction, just because we just don't have, in the United States anyway, these opportunities.

Dr. Hertz-Picciotto: I mean, this particular -- and this goes with so many of the others. Because of the richness of both MARBLES and EARLI both in terms of intensive specimen collection during relevant time periods that have that temporal relationship prior to diagnosis, and you know, I think it's kind of an investment that is -

- it's gone to pass, you know, multiple ways.

So you know, right now MARBLES is funded. But, you know, in 2 1/2 years from now, where will we be? I mean, you know, it's -- some of them aren't, the chunk of really getting information we'll find that's not objectively influenced by maternal knowledge of their child's outcome, which happens in the case [Inaudible] studies is so crucial.

But you know, investing in the EARLI end, [Inaudible comment] cohorts is -- you know, I mean, again, I mean [Inaudible comment] in terms of we're the PIs. But it just seems in some ways like a no-brainer as far as the kind of quality [Inaudible comment] that can come from these studies.

Dr. Susan Daniels: So would it be correct to say that maybe one of the barriers in this area is, you really do need to invest large amounts of money to be able to get the kinds of results you want? You can't do these on a small scale and for low cost?

Dr. Hertz-Picciotto: Definitely.

Dr. Newschaffer: Yeah. And I think there's an

ongoing under appreciation for the resources that are required to build and maintain a cohort like this. And you know, we've learned some lessons and engaged in some streamlining of things. But part of it, it's just an incredibly expensive investment.

You know, some feel that the returns downstream will be there. I guess others aren't, you know, convinced. But to me, and again we are very involved in this work. We think that the investment will be worthwhile. But --

Dr. Julie Daniels: I guess, you know, I'm not directly involved with EARLI or MARBLES. But there have been attempts to retrospectively create the kind of exposure data needed in the large case-control studies. And it's just impossible.

And so I think that even though they are that expensive, that is an investment that would pay off by getting a better signal at the right time period. And so, yeah, I just feel like that upfront cost would really serve us well in the future.

Ms. Redwood: This is Lyn. I agree

wholeheartedly. I really hope something can be done to, you know, provide continued funding of EARLI.

Dr. Susan Daniels: Great. Let's move on to the next one. We've got three left, and then we want to talk a little bit about the aspirational goals.

3.L.B: "Identify genetic risk factors in at least 50 percent of people with ASD by 2014."

And the Committee, last time when they met on the phone, said that the recommended budget appeared to have been met and that further work is needed to identify genetic risk factors in at least 50 percent of people affected by ASD.

And we wanted to get a sense from you in the field about where we are with this right now. What are the current issues? What are the advances in this area, and what are the needs?

Dr. Buxbaum: You know, in the past 18 months or maybe 2 years, with whole-exome data, it's clear that there is the potential, not yet actualized, to identify -- make a genetic finding in 20 percent of kids, just based on whole-exome data.

The problem is that some of the -- you know, we don't yet know when we see a variant, we don't have enough data yet to say this is one that's contributing to risk or not, right? So we do know very clearly by comparing cases and their siblings or cases and controls that there are certain findings, like de novo loss of function mutation, loss of function recessive variation, loss of function on the X chromosome, or small CNVs that just target genes.

Those are higher in autism compared to the controls by about 20 percent. And then when you add CNVs, which is -- you know, depending on whom you ask and how you ascertain, somewhere between 5 and 10 percent, you know, you're getting close to 30 percent. I think 30 percent is a good number.

But we are not yet at a sample size where we can say -- you know, if you see a de novo loss of function mutation -- only 50-percent chance it's contributing to risk in that kid because controls have, you know, some as well, just not as many.

So what needs to be done next, you know, is to do a large enough sample that we can actually

reliably say these are the loci that you can actually comfortably say this is contributing to risk or there is a genetic finding in this child.

So it's both enhancing the 30 percent or making 30 percent real, because right now it's still in potential. And then pushing a little further to get the 50 percent.

Dr. Susan Daniels: Others?

Dr. Buxbaum: I think there's progress.

Dr. Susan Daniels: Great. Any other comments?

Ms. Redwood: [Inaudible comment] where you said that the budget appeared to be met for this objective and it looks like we went way over budget. Our original budget was $33 million, and what's been spent to date is $169 million.

Dr. Susan Daniels: So I was just paraphrasing it. In the table, it says the objective has been met in terms of the -- but I always want to be cautious because sometimes, you know, there are differences between what we see in the actual portfolio data and then how we interpret them. But it's probably fair to say that this one has been met in terms of just the funding alone.

But that doesn't necessarily always correlate with how we feel the intent of the objective has been achieved. But do you have comments on that, Lyn?

Ms. Redwood: Well, I just felt like, you know, we goofed up somewhere if that was what we thought the budget would be for this, to identify 50 percent of people with a genetic risk factor, and we've spent $169 million and we're operating around 20, maybe 30 percent.

So that was just the point, is that we hugely overestimated what the cost would be for that.

Dr. Buxbaum: Well, I think the transition was that, I think, early on a few years ago, there was the thought that GWASs were going to be the way to go, right? And GWASs, the price was kind of well known. And the thought was, if you get 20,000 people, we'll find enough loci.

But what's turned out is that it's not -- it's not the GWASs that are making the findings. It's sequencing. And that turns out to be -- you know, GWASs have been optimized to look very cheaply and quickly at a million loci. But sequencing,

although it's going cheaper than Moore's law [Inaudible comment], it's still pretty expensive. And I think that is where that transition.

I think the assumptions that were made in the original IACC recommendation were really about the existing genetic assays, which were snip genotyping.

Ms. Redwood: Got you. It's really helpful.

Dr. Susan Daniels: Very helpful.

Dr. Hertz-Picciotto: And Joe, do you think that in some cases it may be difficult to identify those genetic risk factors without looking at environments, because of the degree to which gene-environment interaction might play a role?

Dr. Buxbaum: Well, if there was a question, right? I mean, I think, you know, even if there is an obligate second hit, whether it's environment or a second look at locus in the genome, for a certain gene to manifest itself, you're still going to see that first hit more frequently in cases versus controls. So you can find it, but you may not be able -- you may be puzzled when you see it, because you say, hey, half the kids who have

it don't have autism and half do.

And then you can start looking for the interactor, right? But it's about --

Dr. Hertz-Picciotto: Yeah, yeah -- [Inaudible comment]. But it is also highly dependent on how prevalent that, you know, environmental -- you know, if we're going to call it second hit -- is. And it's just highly prevalent.

[Background noise]

Then, you know, you'll treat it [Inaudible comment] the genetic signal [Inaudible comment].

Dr. Buxbaum: Absolutely correct. Absolutely agree. I'm comfortable with 50 percent because it may be hard to get from 50 to 100.

[Laughter]

Dr. Hertz-Picciotto: Yeah.

Dr. Buxbaum: I think you're right. I mean, there's going to be tails on both sides, which are going to be really hard to get, you know, today. They are attainable. And as the environment and genome environment, you know, is further elaborated, we can push past 50 percent of genetic architect risk and also environment risk as well.

But just, you know, because it's going to be hard to get the things on the tails, of what you just mentioned, you know, 50 percent is not a bad target. It puts you solidly into an area where you can think seriously about therapeutics and about pathways and, kind of, what are key drivers for the disorder, without trying to push to a point where you say, well, if I don't understand 100 percent of risk, I can't do anything.

I think it was a wise choice back in the day to say 50. And maybe next time we'll say 70 total risk architecture. And 5 years after that, we'll see how far we got.

[Laughter]

Dr. Susan Daniels: Thank you. That's helpful. Is it okay to move on to 3.L.C? “Determine the effect of at least five environmental factors on the risk for subtypes of ASD in the prenatal and early postnatal period of development by 2015.”

And this may overlap with some of the other objectives. The recommended budget was partially met, and several projects were funded. But it appears there's a downward trend, just based on

the grant data, which again, if there's overlap, that might be a little bit misleading. Epidemiological studies coded other objectives may also represent progress in this area.

So what do you think about this one? How far have we gotten with this in the past 5 years? What are the -- what's the status? What are the needs and opportunities?

[Pause]

Dr. Hertz-Picciotto: Well, I think there's been a lot of work on sort of low-hanging fruit. And you know, there are more than five risk factors for which there are studies. But in any case, it's only study or, you know, one really good study, or many studies and none of them really addressing etiologic time periods.

So it's of concern. There has been a downward trend in funding in this area because I think it's an area that's just really getting off the ground. You know, if you look the last 5 years versus the previous 5 years, it's like a dramatic rise in, you know, what's out there. But there are clues [Inaudible comment] you know, hinting at, what are

the weaknesses in [Inaudible comment] studies and trying to improve this.

There's a tremendous amount that needs to be done. Yeah, and this includes both environmental chemicals, nutritional classes, you know, maternal medical, you know, kinds of conditions. You know, it's neonatal problems and, you know, many others that make sure that those markers are upstream.

[Inaudible comment]

But I think it's an area that, you know, needs a real influx of money, maybe targeted, maybe not targeted. I think there's still a lot more low-hanging fruit we've got to pluck.

Dr. Susan Daniels: Do you anticipate some change in this area because of the change in the *DSM* in terms of subtypes and how the field will be thinking about that, perhaps the projects that would be coded to this in the future could be different because of that?

Dr. Hertz-Picciotto: Oh, let me take back everything I said. I didn't even see the [Inaudible comment]. I think we have [Inaudible comment] at this point in time. And I know I came

into the field thinking, oh, this is really going to be the way. But I think we haven't even started. I mean, maybe a couple of -- a couple of [Inaudible comment]. Yeah. I think that's [Inaudible comment]. I missed that Web site part of it.

Dr. Newschaffer: Yes. So, I mean, to the extent that subtypes are critical to this, you know, I think we've got a long way to go and it gets back to -- if we're talking about, you know, clinically defined subtypes, that's one thing. If we're talking about etiologically relevant subtypes, which strokes back to some of the comments Joe made at the top of the call, you know, we're probably even further away.

You know, we have this issue where there have been some risk factors, where there has been some replication, primarily because it's been low-hanging fruit where the exposure-side data is available in large registries or large databases.

But on the outcome, there's very little subtyping data. And in fact, you know, many of the registry-based studies won't even distinguish

between *DSM-IV* of ASD. They don't think that there's enough validity to do that. And they tend to lump together as ASD.

So while we've got replication on things that could be environmentally mediated like parental age and preterm birth, and now we're seeing, you know, inter-pregnancy interval, those are easily replicated with respect to ASD. We don't have a way forward to try to sort of see whether or not those effects are greater for particular subtypes, because we don't have the subtyping variables linked to those exposures in those large data sets.

So you know, I think that probably progress has been even less than was characterized by the Committee's review here.

Dr. Susan Daniels: Where does this need to go in the future in terms of subtypes and how the field would think about this?

Dr. Newschaffer: Well, yeah. That's a real challenge. I mean, I think going back to some of these -- you know, we'd like to do [Inaudible comment] invest a lot of money in being able to

accurately correct, you know, *DSM-5*'s categories and large data sets. You know, we'd like to know that they were etiologically significant before it goes back to some of the more, you know, fundamental work that Joe was talking about.

You know, you'd like to be able to do some of these things and a completely planned-for and purposeful way. But I mean, I do think that -- I do think that, at the same time, you know, whether it is a shift to *DSM-5* or whether it is just an agreement about being able to capture data on cognitive functioning in a consistent way in these larger industries in addition to ASD or ASD severity in some consistent way that will give us a shot at doing some exploratory subtyping analyses in some of these risk factors that appear to be real overall with respect to ASD, you know, would be worthwhile, even though it is a little bit of a guesswork approach.

While some of the more focused work on trying to see what some of the etiologically relevant subtypes, you know, will prove to be.

Dr. Susan Daniels: Anyone else?

Ms. Redwood: Yeah, this is Lyn. I just -- you know, I think of subtypes a little bit more broadly than just using the *DSM* criteria. And that there are subtypes that you could use such as, you know, the sex. Whether or not their autism presented at birth, or was there a period of regression. You could also break out subtypes for medical comorbidities. So there are a lot of ways to really drill into these subtypes that go beyond just their category of ASD.

So I would like to really see a focus on that, too.

Dr. Susan Daniels: It sounds like this area might be something that the Committee at some point might want to clarify to make it easier for the community to know what's being asked for here. Anything else?

Dr. Hertz-Picciotto: Yeah. Yeah. I think that what Lyn said is a really good point, that there is the -- you know, ASD, PTD, NOS, Asperger's, of course, issues, you know, and *DSM* criteria. But I think these other [Inaudible] characteristics may define the subtypes, which will map differentially

to various environmental factors, might turn out to be fruitful.

Dr. Newschaffer: And the case controls, right? I mean SEED and CHARGE to some extent have been designed to be that kind of subtyping, I think.

Dr. Hertz-Picciotto: Yeah. Yeah. No, absolutely.

Dr. Susan Daniels: So maybe some work is already going on through those studies, which I don't think were coded to this objective.

Alright, so let's move on to 3.L.D. We're just past noon, and I know that you want to finish up soon. We have one more objective, and then I want to talk about the aspirational goals.

"Support ancillary studies within one or more large-scale, population-based surveillance and epidemiological studies, including U.S. populations, to collect data on environmental factors during preconception, and during prenatal and early postnatal development, as well as genetic data, that could be pooled, as needed, to analyze targets for potential gene-environment interactions by 2015."

And the Committee had felt the recommended budget had been met with most of the studies that were in this area being related to cadre. What do you feel has been the progress in this area, the ongoing needs, opportunities, barriers?

Dr. Buxbaum: Well, you know, I think it's true that there are some initiatives here. And iCARE, Minerva, you know, earlier shared these objectives, right, to some degree. You know, it remains a priority, but I don't know what would change about it, but just keep on keeping on.

And I do think that, at the end, the molecular data has to go hand in hand with all the environmental data.

Dr. Susan Daniels: Anyone else?

Dr. Julie Daniels: This is Julie. I'm trying to look at the portfolio as we speak. I mean, I think that cadre [Inaudible comment] that I am not convinced that it's [Inaudible comment]. So I think that, you know, as I said a couple of hours ago, all of these projects that took a long time to get in the field sort of took a long time to get in the field and took a lot of resources to do

so. But they're not finished.

So I think that there has been a lot of support for them, but I guess there continues to be a need.

Dr. Hertz-Picciotto: I notice that cadre [Inaudible comment]. Is that the SEED project?

Dr. Julie Daniels: Yeah.

Dr. Hertz-Picciotto: Okay.

Dr. Julie Daniels: Yeah. So I mean -- yeah, I don't discount that there's been a lot of resource put toward that. And those data are just now ripe for analysis. So I think that most of the funds have been to support the data collection and study infrastructure and not necessarily the analysis. And so that's what needed going forward.

And now I think I'm looking at the right thing. Sorry.

Dr. Susan Daniels: Okay. Great. Well, let's move on to -- just have a few minutes of discussion about the aspirational goal. I know it's after the hour and some people might need to get off the phone. But we wanted to have a few minutes, at least, to talk about the aspirational

goal.

"The causes that ASD will be discovered that inform progress and treatments and lead to prevention preemption of the challenges and disabilities of ASD. And this was the overall goal that the committee had for research in this area, that it would go toward eventually leading to treatments and prevention."

So where do you think we are in terms of how this is progressing? And we've already had, you know, a lot of discussion over the past couple of hours that kind of play into this. But any specific thoughts about this?

[Pause]

Dr. Susan Daniels: Anyone?

Dr. Newschaffer: Is the idea to kind of update it somehow?

Dr. Susan Daniels: Just to get a feel of, how far have we come in terms of meeting this aspirational goal? It sounds like, from -- to me, as -- I've listened to all of you speak about this, that we haven't come terribly far. That many of these areas are still in their infancy, and a

lot needs to happen before this would get to a translational phase, that we're still in the early parts of developing the field. But --

Dr. Newschaffer: I think that's right. I think causes are being discovered. How they inform prognosis and treatment into that translational phase is still in its very, very early days. And of course, prevention and preemption and curing -- ultimately possible that that's a next step that we're still quite far away from.

Although, you know, if you take specific well-defined etiological subtypes, you could say with fragile X, you know, say what you want about the Seaside trial, but most people think that there was some activity there that [Inaudible comment] was effective in a subgroup, right? And so there are some translational examples, but they tend to be when autism is looked at from a very kind of high perspective of etiology.

So some progress, but not anywhere near what we had hoped.

[Several speakers]

Dr. Buxbaum: I think we need to urge patients.

I think, you know, especially when we think about this kind of aspirational goal, it's critically important. But we've heard throughout the 2 hours that also, with some of these research objectives, that there's a little bit of a tendency. We've made these investments, and I don't think there's a full appreciation that, you know, the amount of time that it takes to sort of cultivate these investments in this area for a lot of the reasons that have come out here.

If we think about the genomic side, which we've talked a little bit about, maybe less than the environmental here, you know, with all the molecular biology revolution and the trends, the breakthroughs that technology has provided, we have made advances, but maybe not as much as we thought.

And on the environmental side, we really need to be extra patient so that we can accumulate some of the benefit for the investment that we've made over this last decade. And that's got to come through somewhere.

Dr. Julie Daniels: Yeah. I'd like to echo that

completely. I was about to say a very similar thing. I think we can look at it as the glass half full in the sense that we have made progress in creating some infrastructure in which we can start to really dig in. And without the infrastructure that was there, that would be impossible. But I think that's been, you know, the necessary investment so far and set the stage for the future.

Dr. Newschaffer: We need to keep investing in it. Because we've heard a few times about how, you know, [Inaudible comment] maybe being cut off a little too prematurely, and that would be a terrible shame.

Dr. Buxbaum: And then on the flip side is, of course, managing the expectations, right? You know, there's the feeling in the field that a lot of promises -- in the community -- that a lot of promises were made and weren't hit. Then there tends to be a backlash, right?

Dr. Newschaffer: Oh, yeah, no doubt. I think that would be a mistake. I mean, I think that the overarching theme of complex etiology, you know,

resonates across everything. And you know, there's unlikely to be big genes. There's not likely to be, you know, cigarette smoking and lung cancer here. And I think we all understand that, and we have to manage those expectations.

[Several speakers]

Dr. Susan Daniels: How can you compare this to other disease fields in terms of, you know, with what we have for autism versus maybe what they've had over the past 25 years for cancer or Parkinson's or some of these other diseases that might have been studied in more depth earlier on? Do you think autism has maybe less or more infrastructure in place to try to make those discoveries about etiology?

Dr. Hertz-Picciotto: Well, you know, I was on the breast cancer and the environment IOM panel. I chaired that panel. And that was in whatever, 2010 or 11 or something like that. And one of the things that was really striking was that after 20 years of research, there was actually not a lot of progress in identifying -- you know, there was some on the genetic side. And not that much new

that had been learned on the environmental side, which was really quite a, you know, I think a disappointment.

So when I look back at the last 5 years in autism research, I actually think -- you know, we've made -- we have put in place a lot of infrastructure and that we're in a really -- you know, optimistic [Inaudible comment] as long as the funding doesn't drop off. And in fact, I think it truly does need to increase so that, you know, while we have now six or seven studies on air pollution and autism, as I mentioned earlier, that's because, yeah, you don't have to go out and reinvent exposure assessments for that. You don't even have to ask that many questions to get that kind of data. And you don't need biosamples, you know, for the studies.

Some people might say we do need biomarkers. But in any case, you can do research without them. That's not the case for many of the endocrine-disrupting compounds or many of the other sorts of -- where the environment is the home or the products being used or food the mother is eating

or the child is being given.

So I don't -- you know, with that comparison, I think when I was on that committee, I was shocked by how from 20 very intensive years of research into environment and breast cancer, because where I was raised in the '70s, didn't seem to get it. And one of the issues raised in cancer studies in our final report was for problems in even [Inaudible comment]. That's actually --

Dr. Susan Daniels: We're losing you, Irva. We can't hear you well.

[Pause]

Dr. Hertz-Picciotto: -- that we can do studies in shorter time periods and [Inaudible comment].

[Pause]

Dr. Buxbaum: Well, I think Irva was probably saying that there's been a lot of progress, and there are a lot of things going on.

And I share that also for the more molecular side, you know. Everybody will applaud when I say that I think that, you know, we are going to -- you know, with the current studies and a few more

hopefully coming in soon -- we are going to be getting close to 50 percent. And, you know, that's a big deal. And I think that we're not too far away from that.

And the applause is that then more money can go to gene and environment, and environment solely, right? I think that kind of the gene discovery part in autism, you know, we are making a lot of progress. And I think in the next 3 to 4 years, we'll be at a critical place, a critical phase, where we can say I think we're getting close to those numbers, right, that aspirational goal which reduced to a specific kind of, you know, discovery and 50 percent of kids are individuals with autism. You know, we're not too far away.

Dr. Newschaffer: I mean, this just gets metaphysical. But I mean, I think that that is one achievement, no doubt. But you know, again, you're talking about managing expectations, I think that there's not an understanding that those genomic markers are not necessary and sufficient causes and that, you know, it doesn't necessarily

represent that, you know, we solved the etiologic puzzle in 50 percent of the cases at all.

You know, there are other component causes, probably many yet to be discovered for the vast majority of that 50 percent --

[Several Speakers]

Dr. Buxbaum: -- the word genetic finding rather than genetic cause, because they are just findings, right? But I think that -- the way I --

Dr. Newschaffer: Not that the public understands that, which is part of the problem.

Dr. Buxbaum: Good point.

But as we articulate the goals for the NIH, if you will, or for the IACC more broadly, you know, having specific goals, we have to interpret, explain what the goal actually means. But I think it's not bad to be coming up on that number because --

Dr. Newschaffer: Oh, absolutely.

Dr. Buxbaum: -- even if it doesn't explain all the risk, it gives the neuroscience community hundreds of tools to go on to the more translational questions.

Dr. Newschaffer: You're right. Absolutely, and you know I wish we were at 50 percent with that kind of attribution on the environmental side. I do.

[Laughter]

Dr. Newschaffer: So, no. It's definitely a marker of progress. No doubt.

Dr. Susan Daniels: Any other comments as we try to wrap up this part of the session?

Well, you've all had a wonderful discussion. We really appreciate everyone sharing their thoughts about these objectives and your overall assessment of the field. At the workshop on Friday, I will be sending you information about the workshop. The agenda is already posted online, and I'll send it out to members of this Group.

We will have about 50 minutes to talk about Question 3, but as you can see, we've spent a couple of hours here going in more detail to talk about the Strategic Plan. And we're going to be trying to think a little bit bigger picture in the workshop about, what are the overall take-home messages, and where do we go next?

And so, I think with that, we're ready to finalize this call unless there are any other questions or comments anyone has. We appreciate you staying a few extra minutes to finish up the discussion.

[Pause]

Anything from anyone?

Dr. Buxbaum: Thanks very much.

Dr. Susan Daniels: Thank you so much for being here. We appreciate it.

[Chorus of "thank you" and "goodbye."]

(Whereupon, the Strategic Plan Question 3 Planning Group was adjourned.)