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INTERAGENCY AUTISM COORDINATING COMMITTEE

SUBCOMMITTEE FOR
BASIC AND TRANSLATIONAL RESEARCH

STRATEGIC PLAN QUESTION 1 PLANNING GROUP

CONFERENCE CALL

TUESDAY, NOVEMBER 12, 2013

The Strategic Plan Question 1 Planning Group convened via conference call at 2:00 p.m., Susan Daniels, *Executive Secretary*, IACC, presiding.

PARTICIPANTS:

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SHANTEL MEEK, Administration for Children and Families (ACF)

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PROCEEDINGS:

Operator: Thank you for standing by and welcome to today's conference. At this time, all participants are in a listen-only mode. Today's call is being recorded. If you have any objections, you may disconnect.

I will now introduce your conference host, Dr. Daniels. You may begin.

Dr. Susan Daniels: Good afternoon and welcome to our listening audience, to members of the IACC, and to our invited participants for joining us on this call of the IACC Strategic Plan Update Question 1 Planning Group that is going to be talking about the update to the Strategic Plan.

We are going to be going through today a couple of items that I have sent out to the members of this Group and that are posted on our Web site. For those of you who are listening, if you go to the Meetings and Events page of the IACC Web site, you will see this conference call from 2:00 to 4:00 p.m. listed. And if you go to the link for Materials, you'll find the documents that we

have shared with the IACC and our invited participants there and you can follow along.

So there are two documents: One is called the Cumulative Funding Table, which we discussed on the previous IACC call, and I provided it as a reference. And then today, we're going to be talking about the Conclusions Table, which is the second document.

But before we get started, I'd like to take a roll call so that everyone can hear who's on the phone. And we will be posting bios of the invited participants up on the Web site before the workshop on Friday. We also do have bios for all the IACC members on our Web site.

So let me go through the roll call. Anshu Batra is not going to be able to join us today.

Coleen Boyle?

Dr. Coleen Boyle: I'm here.

Dr. Daniels: Thanks.

Gerry Dawson?

Ms. Geraldine Dawson: Here.

Dr. Daniels: Thank you.

Alice Kau is not going to be able to join us today.

Shantel Meek for Linda Smith?

Ms. Shantel Meek: Here.

Dr. Daniels: Thanks.

John Robison?

Maybe he'll be joining us later.

Lisa Croen?

Ms. Lisa Croen: Here.

Dr. Daniels: Thank you.

Ami Klin?

Maybe he'll be joining us later.

Karen Pierce was not available today. And Dennis Wall said that he might join around 3:00 p.m.; he is traveling today.

So those are the members of our Group. Today our goal is to go through the nine objectives in Question 1 of the Strategic Plan to talk about progress that's being made in the field.

Last time we got together, we had the IACC members go through each of the objectives and look at the status of each objective in terms of what kinds of projects have been funded, both by the Government and

nongovernment funders in this area, and to assess whether in terms of projects that were recommended, whether those things had occurred, whether they had been funded, and if the projects that had been funded were covering the objectives as intended by the Committee.

And so, they developed -- we developed -- some conclusions based on what was said on the previous call. And so those have been summarized in the table, the Conclusions Table that I've provided for you.

On this call, we want to get input especially from our external experts who are on the phone with us about the overall status of the field in each of these areas. What have been the scientific advances in each of these areas? What are the needs, remaining gaps, and barriers in each of these areas?

And so we welcome you to chime in and share in the discussion about each of these.

Do you have any questions before we start?

[Pause]

Okay. So I'll go ahead and start with

the first one, which is Objective 1, short-term A, 1SA: “Develop, with existing tools, at least one efficient diagnostic instrument (for example, briefer, less time intensive) that is valid in diverse populations for use in large-scale studies by 2011.”

The Committee members who were on the call last time thought that the recommended budget for this objective had been met and that the remaining gaps include the need to develop instruments that target diverse populations and to continue working toward developing instruments that are ready for broad deployments.

So what do you think is the state of the science in this area? And what are the remaining gaps and needs and barriers? What are the thoughts of the Group?

[Pause]

Dr. Dawson: So, I have a question. This is Gerry. And so I'm just looking at some of the -- can you hear me?

Dr. Daniels: Yes.

Dr. Dawson: Okay, so I'm just looking at some of the projects that have been funded.

And you know, it's great to see the level of funding here. So you know, one of them in particular I know that people have been very interested in a briefer version of the ADI-R. And of course, there is one project there, Cathy Lord.

But you know, I guess I'm just wondering whether we really have met the objective, though, because I'm not aware that that has actually been, you know, completed and validated. Is it in process still? I mean, I think that we've met the funding objective. But have we met the objective I guess is the question I have.

Dr. Daniels: That's the -- part of the Question was addressed on the last call. Just in terms of the funding, that the Committee had felt that the recommended budget had been met and that some of the work was started through the projects that have been funded.

But really the goal on this call is to talk about, where is the science? Have you met the intended goals of this objective in terms of the advancement of the field? And what remains to be done?

Dr. Dawson: Right, so I'd be curious what other people feel on the phone. And perhaps I'm just, you know, not up to date. But I'm still sort of waiting for that validated short ADI. And I'm not -- is it out there? I know that she's -- I know Cathy has been working on it. But where does it stand now?

Ms. Meek: This Shantel from ACF. I would second that thought, that I think the funding levels have been met, as we discussed in the last meeting, but not necessarily the objective. And I would just point out, not only an abbreviated ADI-R or other tools, but also ones that have been validated and found to be reliable in diverse populations, I think is also another gap.

Dr. Croen: Yeah, I agree with that. This is Lisa Croen, and I agree with both those comments. In reading through the funding table, you know, looking at the specific projects, there are a lot of projects that I guess the -- how are those projects linked to each objective? Is it what the PI on the project said they were addressing in terms of

the IACC?

Dr. Daniels: So the OARC reaches out to each of the funding agencies, and the funding agencies and organizations come back with proposed coding for the projects. In some cases, if they ask, OARC does preliminary coding, and the agencies and organizations confirm whether or not that coding is correct, to the best of their ability.

And the [inaudible comment] in each project attached to one of the objectives or put it in the “Other” category or such an area. So we only allow coding to one objective for each project. So there are cases in which a project that was broad that might have applied to more than one objective, it's only categorized in one place.

So that avoids the issues that come up when looking at the funding numbers. And that's why that information is not -- one reason that it's not -- complete, as we also consider what the state of the science is and what's going on in the field.

Dr. Croen: Okay. Given -- reading the

titles and some of the little blurbs for those projects, I think that, you know, there's obviously been a lot of funding given. But I agree with Gerry and the other person -- I didn't catch your name -- that the objective of finding, of developing new tools that are more efficient and can be used in a diverse population I don't think has been yet -- at least the result of those studies that have been funded have not been -- they haven't all been completed, I think, those studies. So it's hard to tell what they've come up with.

Dr. Klin: This is Ami. I would actually state the same -- plus. And the plus is that one of my concerns is that some of the instruments, even those instruments that have been validated for those standards, are really not used very often in community-based assessments.

My sense from the CDC data is that the ADOS and the ADI are using fewer than 2.5 percent of the assessment that takes place in the community. So when we talk about something that is used in diverse

populations, I believe that this is a challenge that one has to embrace, the fact that even when one does have a validated gold standard, they are not used with diverse populations.

Dr. Daniels: Is that because of the ease of use, or is it because of other reasons? Can you elaborate further?

Dr. Klin: I believe that it's very costly, costly from a whole range of perspectives. In order for those instruments to be gold standard, the people need to be trained to standard. And that's very, very, very costly. And reliability needs to be maintained, and that's very costly. The procedures take a long time, and that's very costly.

And sometimes the gold standards that we adopt in university-based research centers are simply not viable in the vast majority of clinical environments where children are seen. So that gap, to my mind, is a real challenge.

Dr. Dawson: Just to kind of second that issue, and maybe, you know, try to clarify

too what the need is here, if you want a diagnostic instrument that's efficient, cost effective, could be used in large-scale studies, it really does need to be able to be used in community settings.

And I think one of the problems with the existing tools is not only are they long, but when they're using clinical settings, people actually aren't trained to reliability. And they use them, I think, in a very variable way. And so, you know, even the existing tools, when they're used out in the community, are being used in such a diverse way because they're so complex, they're very hard to standardize in a clinical setting.

So you know, I think that if you read, for example, Cathy's project, you know, I just drilled down in her abstract. It does seem like she's working toward the goal that we're talking about. It's just that I don't think that that data is out there yet.

And then even after we develop those in one study, to validate it across a lot of different populations is a whole next step in the research process.

Ms. Meek: This is Shantel from ACF. Just to add, the Question says "screening and diagnostic tools." And I think it's important to, you know, distinguish those and pay attention to both of them. And I think that really influences the extent to which we encourage community-based centers, whether early-childhood centers or community clinics or others, to use these tools; so screening tools might require less training than, you know, diagnostic tools.

And so, not only the validation of screening and diagnostic tools in diverse populations of children, but also looking at how we disseminate both of these techniques to the appropriate community-based settings.

Dr. Boyle: This is Coleen, too. I'm actually standing by to hear from our experts. But I guess one thing I had noted, going through a number of years of funding, is that the majority of the funding seems to be going to the screening tools versus the diagnostic process.

So I mean, that's just, again, something perhaps to note as we think about revising

this and thinking about the current state of, I guess, the art in terms of identifying autism.

Dr. Klin: I would second that. It's Ami Klin. I think that what the extent of this here right now is that there is a whole range of things that are associated with trying to capitalize on the advances in screening. We see that a lot of folks who are screened positive are not engaged in treatment. That I think some of our emphasis needs to start going to improving access to care.

But also understanding some important factors that would make screening more useful, such as parent engagement and so forth. So I would agree. I think that there is just as much -- I remember sort of once learning how to -- how to administer the developmental assessment. And there is so much in common among the developmental assessments simply because there is just as much as babies can do.

I think that we're getting to a point in screening that the work has been done, to some extent. What we need to do is how to

capitalize on that and how to move on from screening to diagnosis and from screening to access to care.

Dr. Boyle: Yeah, and maybe, Ami, just picking up on that a little bit, you know, and taking some of the screening instruments and integrating them within the context of, you know, primary care, or ongoing assessments of children to see really how they work in the real world.

Dr. Croen: Yeah. This is Lisa. I think that's one of the big challenges -- is that, you know, we do have some fairly decent screening tools that are free and, you know, can be used but they're not. The uptake of them in the community is really poor. And even organizations that are very dedicated to early developmental screening, it just isn't being done to the extent that it should be. It's not universal by any means.

And so there's a lot of work to be done to figure out how to increase the utilization of the screening tools.

Dr. Klin: Yeah. So in a way, I think it would be nice -- this is just a suggestion –

is that we know, probably more efficiently now, how to go from screening all the way through engagement of family in early treatments. There are several different important aspects of it.

And my suggestion would be that one starts moving into those areas and incentivize the study and the advancement of knowledge about those specific things so that we can truly make screening helpful for families and for communities.

Dr. Dawson: So just to comment on this -- two points. Just to underscore this idea about families following up on screening, I thought one of the most interesting results in the Karen Pierce study of screening in primary-care practices was that only 60 percent of the children who screened positive, their parents actually followed up and sought a diagnostic evaluation. And so, there is this huge gap.

But there has been -- there was an RFA that went out this year from NIH that was looking specifically on service interventions that would lower the age of early detection

and access to care, that did, I think, target, at least to some extent, the kinds of issues that we're bringing up. So you know, when we update the Plan, we'll probably want to note that.

Dr. Klin: Yes. It was a fantastic RFA. In fact, it was so focus entirely on parent engagements. And so, I loved that. And it was such a detailed RFA that people need to work very, very, very hard to address [inaudible comment]. It was great.

Dr. Dawson: Yes. And I should point out that Autism Speaks also had a similar RFA that went out earlier in the year on early access to care or their early access to care RFA. So they read -- you know, it was really a very similar, I think, intention behind those. So those two organizations that have at least recognized this and tried to solicit proposals.

Dr. Klin: But to go back to the point that was made before, we have -- we probably are getting to some kind of acid test in terms of questionnaires used in screening as screening tools. I'm not sure that we have

the ideal diagnostic tool yet. And we certainly don't have any performance-based screening or diagnostic tool.

Dr. Boyle: Yeah, I agree. But I think that's a good summary, where we are.

Dr. Dawson: So what do you mean by “performance-based,” Ami?

Dr. Klin: A little bit like this: If I'm concerned about my child having cancer and I take my child to a physician, I'll be surprised if the physician got to me and said, "In order for me to screen or diagnose your child, you need to complete this questionnaire, and I'm going to use this questionnaire as a big – so of a big factor in my decision."

What I'm saying is that I think the science of autism is such that we take our children to physicians, and physicians give us questionnaires. I think that that's not going to be sustainable over the long run. Eventually, autism is going to have to catch up with the rest of medicine, and we will have to have something that is performance based --

Dr. Dawson: Okay.

Dr. Klin: -- meaning something that the child completes.

Dr. Dawson: Got you. Well, so I would say the STAT, you know, would be considered a performance-based screening tool, you know, that we do have at least some evidence for that one.

Dr. Klin: Correct. It's not a lab, but it is performance based, yes. It's based on the child's behavior. But I think eventually we'll have to progress to some kind of a lab sort of test.

Dr. Croen: One more comment about screeners. I think there are many, many different screeners. But the applicability of those screeners in different kinds of populations -- low-literacy populations, you know, non-English speakers, people in different countries -- I think are inadequate. So I think there's a lot more work to be done to develop some instruments, both screening and diagnostic that are very low cost or free and that are applicable in these diverse settings.

Dr. Boyle: The other point, Lisa, on that one maybe, too, is that the younger we go, the less likely it is that it's parents raising the concern. And then the less likely they are to follow up or, you know, react to that concern.

Dr. Daniels: Great. Anything else that you have to add to this one?

Dr. Dawson: Susan?

Dr. Daniels: Yes.

Dr. Dawson: Susan, may I ask a question about procedure, since I know that at some point there's a writing task that evolves out of these exercises? Is somebody taking notes?

Dr. Daniels: Yes. So OARC is taking notes. We're going to update this table that we've provided for you with more information from this call. And that will be available on Friday at the meeting. And then, after that, we'll assign the writing tasks. Everything got shifted because of the shutdown, and we weren't able to do -- we weren't able to have members of the Committee turn in writing assignments before.

Dr. Dawson: So -- but in terms of notes,

is somebody taking notes that are pretty detailed about the conversation that's occurring? Or more just updating the table?

Dr. Daniels: We are taking detailed minutes. But at this point, we're a little bit backlogged with those minutes. So it's not going to -- those aren't going to be ready for you on Friday.

Dr. Dawson: Okay.

Dr. Daniels: So we will have them, and we do -- we have transcripts. Those are going to take much longer. But we do have minutes. But we're trying to update the tables with kind of briefer information so that you have, at a glance, the gist of the conversation and the major points that were made.

Dr. Dawson: Okay. Great. Thank you.

Dr. Daniels: Hopefully, whoever ends up doing some of the writing will also remember part of it. But we will have minutes. It's going to take a little bit longer to process them, though, because there are 12 sets of minutes.

Dr. Dawson: I'm going to start taking some notes.

Dr. Boyle: Yeah, me, too. I was going to say it's nice to have the details of the conversation.

Dr. Dawson: And you know we're going to be doing the writing, right, Coleen?

Dr. Boyle: Yeah.

[Laughter]

Dr. Dawson: Okay.

Dr. Daniels: All right. So let's move on to 1.S.B: “Validate and improve the sensitivity and specificity of new or existing screening and diagnostic tools, including comparative studies of general developmental screening versus autism-specific screening tools, in both high-risk and population-based samples, including those from resource-poor international settings and those that are diverse in terms of age, socioeconomic status, race, ethnicity, gender, characteristics of ASD, and general level of functioning by 2012.”

And the Committee, last time they met, felt that the recommended budget for this objective had been met in terms of the project, and that more diverse populations

were addressed in this objective. However, comparative studies between general developmental screeners and autism-specific tools were not in the pool.

And so what do you feel is going on in terms of the state of the science in this area? What are the current advances, needs, opportunities, barriers?

[Pause]

Dr. Klin: I don't know the extent to which Amy Wetherby has published some of her new work. But there is a direct comparison in a fairly diverse population in more than one site, the comparison between a broadband developmental screener tool versus an autism-specific one.

So I think, to my mind, she's the only one who is doing that. But those data would be very interesting and the extent to which she has been able to actually help us understand the percentages of children being screened positive for general developmental concern, and then moving on to an autism-specific, it would be great. So maybe somebody knows more about that than I do.

Dr. Daniels: And Amy Wetherby will be part of the workshop on Friday.

Dr. Klin: Um, hmm.

Dr. Daniels: So if not before then, you might be able to get some information from her on that day.

Dr. Klin: Um-hmm.

Dr. Boyle: Does anyone else know of anything else going on besides that?

Dr. Klin: Well, I know the work that Diana Robins is doing in Atlanta in one particular primary-care center, because it's affiliated to our mother ship. It's [inaudible comment] Children’s Healthcare of Atlanta in Atlanta. It's about 90-percent African Americans.

And a major concern there is that -- has been what we've discussed already. There was a great success in implementation. In fact, it is a directive that every physician needs to implement that screening, using the M-CHAT, and great concern about the fact that even families that were offered free evaluations did not follow through with that request, so, let alone sort of accessing

care. It's what we discussed before. That's all I know.

[Pause]

Dr. Boyle: It sounds like maybe Amy will provide some more specifics on this objective on Friday.

Dr. Klin: Yeah. Amy put together a program, a multisite L.1 with Craig Newschaffer, with Cathy Lord and ourselves here, for the L.1 that you had mentioned before. And she had to summarize over those data for that particular grant submission. So I think she will be in a good position to let you know.

Dr. Daniels: So that project is likely either coded elsewhere. Or maybe if it's newer, it might not be in this pool?

Dr. Croen: It sounds like it was a new grant proposal just submitted to that Health Services RFA. Ami, is that what you're --

Dr. Daniels: That wouldn't be reflected.

Dr. Klin: -- that is correct.

Dr. Croen: Yeah.

Dr. Klin: You know, I just mentioned the submission only because she would have had to

summarize the data she has on her screening tools, the broadband as well as the autism-specific, for definition.

Dr. Daniels: So if there is a funded project, which it sounds like there is, if it's not reflected in this pool, it must be somewhere else in the Plan.

Dr. Dawson: One question I have is -- so it sounds like that there has been some improvement in terms of, you know, the number of studies that are looking at issues related to candidate validity if some of these tools in different ethnic minority populations in the U.S.

But I can't imagine that there still isn't quite a bit of work that still needs to be done internationally.

Dr. Boyle: Shantel, are you still on the line?

Ms. Meek: Yes. I was going to --

Dr. Boyle: Yeah. Did you want to talk about the survey of well-being in young children?

Ms. Meek: Yeah. So the survey of well-being in young children out of Tufts

University, I don't know how familiar folks are with it. But it's a development and behavioral screener that has an autism component to it. So it's developmental, behavioral, it has an autism component, and it also has a family risk index.

And it's still in development. It has some data in clinical settings. It's a parent report. And it is being made to be in the public domain, so -- free of us. So ACF is -- and the CDC -- together are working to do a couple of things with the [inaudible comment]. So one of those is to make it electronic so that it’s sort of validated across different settings, including early-childhood settings.

And the second is that we're funding a really small study on Native American reservations, looking at the cultural appropriateness of the survey for well-being of young children in Native American populations home visiting programs. So that was just funded a few months ago. So that is underway. So we should, you know, have preliminary results in the next year or so.

Dr. Boyle: And not quite what you were talking about, Gerry, but just an attempt to look at other populations, diverse populations.

Dr. Dawson: No, that's really helpful.

Ms. Meek: And I mean, there's also the opportunity, because it's an autism-specific screen, and then it also has a general developmental on behavioral domain to compare those two. In terms of the part of the Question, looking at general screens as they compare to autism-specific screens.

Dr. Klin: Gerry, I just wonder -- I know that you're no longer at Autism Speaks, but do you still recollect all of the studies that Andy Shih is orchestrating around the world? Is there one focused on early screening?

Dr. Dawson: Well, there's not one. And there are, you know, in many countries they have translated the M-CHAT, for example. And they're being used in different studies. But I certainly -- I don't think that we could say that those have been validated in any sense, or at least not in very many

countries, in the way that we would think of that word, you know, here in the U.S.

The other thing is that I do know that the WHO had a meeting recently. It was in October, early October, where they kind of did a state of the science around autism, and specifically, part of that was focused on screening and diagnosis. And it might be helpful to try to get a readout of what was discussed in that meeting.

Dr. Boyle: I know Cathy Rice attended that. So perhaps she'll be at the meeting on Friday. And the focus was much more on the need to embed children and child developmental education. More generally, that's about as much as I know about it.

Dr. Croen: I know I knew from international colleagues that, you know, there's a lot of talk about the need for free or very, very inexpensive tools in international settings, but that work in their context. And you know, the costs associated with these different tools -- M-CHAT is free, but that's, you know, maybe one of the few ones that is.

It just prohibits them from using these things in their settings. And that's a real roadblock.

Dr. Boyle: Yeah.

Dr. Croen: I think the other roadblock is just the -- many of these tools have been developed for white or Western cultures. And they just may not be getting at the kinds of issues that you see in other settings. And so there's a need for tailoring or, I think, developing some tools that are validated in other kinds of diverse settings.

Dr. Boyle: Yeah. And I agree. And I think the other part of the WHO was -- and this is really important -- is really how to support caregivers in a low-resource context --

Dr. Croen: Um-hmm.

Dr. Boyle: -- you know, with a focus on monitoring child development instead of screening to identify or label.

Ms. Meek: Sorry.

Dr. Klin: I'll speak right after you.

Ms. Meek: No, go ahead, please.

Dr. Klin: I think that, as the field has

evolved a little bit from needing some kind of a questionnaire screener to actually understanding what we want that screener to do, we probably have a more sophisticated view of what the real challenges are going to be.

And I think that somewhere in this Plan, there has to be room for a sort of -- it starts talking about parent engagement. But it's really a training component, a tool that brings together elements in the community that are going to, hopefully, work together toward a different way of doing things.

I think that those three elements, primary-care centers -- particularly, primary-care physicians -- early intervention provided within families, one of the big issues that I just heard that is a problem internationally is that you can have a screener. But if people are not speaking the language -- I don't mean the language of the country, but the language -- of concern about child development -- then you don't have much of a chance that this is going to have an impact on the community.

So to make a long story short, I think that we need other ways of training trainers. I think that we need other ways of bringing important factors of the community together and the common language, the language of what I think I just heard Coleen mention as concern about child development.

Ms. Meek: Yeah, this Shantel, I couldn't agree more. And also just to emphasize that -- and I think it has been emphasized that resource-poor areas are not only international, but we have plenty of them here at home, and we see those with various numerous, numerous early-childhood providers, childcare providers, home-based childcare providers.

On reservations and otherwise in resource-poor areas, we see the cost-prohibitive nature of many of these screens, where we play a factor in how much and whether they use valid and reliable screening instruments or not.

And you know, just to echo what Dr. Klin just mentioned as well, just the need to -- while we have some screens that are valid and

reliable, we really need to make them usable or applicable to people with -- that aren't necessarily trained in autism or don't have degrees -- very low, you know, lower scale individuals who do watch children day after day and are at a really good -- in a really good position to notice a lot of these initial screens.

Dr. Daniels: Great. So can we move on to the next one? I'm worried about you running out of time because we've been spending about 15 minutes per item here.

[Laughter]

And we need to get through. I don't want you to run out of time and not be able to get through all of them. Plus, we wanted to have time to talk about the aspirational goals.

So let's move on to the next one: 1.S.C: “Conduct at least three studies to identify reasons for the health disparities in accessing early screening and diagnosis services, including identification of barriers to implementation of and access to screening, diagnosis, referral, and early-intervention services among diverse

populations, as defined by socioeconomic status, race, ethnicity, and gender of the child."

And the last time the Committee met on the phone, they felt that the recommended budget had been partially met and that the projects supported here were the beginning of the work that needs to be done, but more needs to be done. And that the studies coded to this objective don't focus on identifying reasons for the screening and diagnosis disparities, but rather are focused on developing tools to address the disparities. So what are your thoughts about this area? What's the state of the field here? What needs to be happening in this field? And what are the major barriers?

Dr. Klin: If I may jump in first because this is an area of great frustration. I feel that two or three, four people have made fantastic contributions. And I still believe that the sophistication of this research pales in comparison to what has been done in other fields, like AIDS prevention and like -- I have colleagues that I'm trying to twist

their arms here to sort of work in the field of autism.

[Inaudible comment] there are two professors who have done incredible research in AIDS prevention, with [inaudible comment] and in other minority populations. So I don't think that the CDC can do [this] all by itself. I think that there has to be a requirement for greater sophistication in this research, and I believe that that should be reflected in the RFAs that are going to come out.

Dr. Dawson: Ami, can you elaborate a little bit?

Dr. Daniels: There already are RFAs that are planned. So just to be clear, we're just talking about the Strategic Plan, which is the advisory document.

Dr. Boyle: Susan, you fade in and out. I don't know if you're away from the phone.

Dr. Klin: Me?

Dr. Boyle: No, no. Susan Daniels.

Dr. Klin: Oh.

Dr. Daniels: I'm right here at my colleague’s office.

Dr. Boyle: Yeah, sorry.

Dr. Klin: Maybe Coleen can help me out here. I think that what we have in research is saying, whether or not ethnicity plays a role and race plays a role and it plays a role in this situation, but not in that situation; to my mind, this is the extent of what has been done, but only a few studies.

We have done very little in terms of, how are we going to be more effective in particular cultures? So maybe Coleen can help me here. The work of Ralph DiClemente in AIDS prevention, to my mind, is a model. And I would love to see some of that sort of happen in autism.

There is a leadership institute here in Atlanta run by David Satcher and Martha Okafor that they are developing new tools, not to develop a screening for a particular condition, but to empower parents in certain communities to take upon themselves the empowerment of others -- this kind of stuff that basically comes up with specific recipes for making -- for advancing this in real cultures, in real situations.

Dr. Boyle: Yeah. I mean, I think those are great examples. And you know, I think we're at the point here where we're describing what's going on, but we are not at the point where we're actually trying to understand the barriers and how to, you know, how to move forward.

The example you gave earlier with Diana Robins and the challenges of sort of moving the screening process along and empowering parents, I mean, those are really, really challenging questions and things that we need to be working and putting our energies into as the next step.

Dr. Dawson: Great. Thank you.

Dr. Klin: I should stop talking a little bit.

[Laughter]

Dr. Dawson: No, no, no, no. That was really helpful. I'm being -- I'm a little quieter because I'm trying to take notes.

Dr. Croen: I mean, I'm just looking at the projects that are listed under this objective, addressing this objective. And I would agree that I haven't seen much research

trying to really understand, you know, the way this objective is written, understanding the barriers that families are facing in accessing or utilizing services that they may have ready access to. What really is going on?

And I think some of those studies by design have to be more qualitative. And it's very difficult to get qualitative-type studies funded. That's one -- you know, I've experienced that. And so that may be part of the problem, is that we're using in review of these projects that are really trying to get at some of this more nuanced, you know, information, that requires going to talk to people in a kind an unstructured way or semi-structured way, they don't -- they're evaluated pretty critically and don't get funded.

Dr. Boyle: Yeah, I agree with you, Lisa. I mean, it's definitely the sort of behavioral motivation type. And many times it's the qualitative, the quantitative work that are put together, but that qualitative piece is really, really important.

Dr. Croen: Yeah. Um-hmm.

Dr. Daniels: Anything else on this one? Great. Let's move on to 1.S.D: “Conduct at least two studies to understand the impact of early diagnosis on choice of intervention and outcomes by 2015.”

And from looking in the portfolio, it looks like, to the Committee and to us, based on the coding that we have, that no projects have been initiated in this area, although there could be overlap with some projects that are coded to other questions or objectives throughout the Plan.
Possible barriers that the group thought of on the last call were the difficulty of finding a late diagnosis cohort for comparison and the more general difficulties of carrying out large longitudinal studies.

So what do you think is holding us back in this area?

Dr. Dawson: So if I remember the history of this, that this was an objective that a number of the self-advocates wanted. Is that right?

Dr. Daniels: I don't recall that.

Dr. Dawson: Yeah. I think that the issue here was that people were real -- and I could be wrong. So please, you know, forgive me if I don't remember the history of this. But I do think that the Question was about different methods of intervention, right? So teach versus ABA.

Dr. Daniels: Right.

Dr. Dawson: And I would say that there's been a couple of things. One is there is a study published out of the UNC group, where they did compare some different preschool programs. I think it was the LEAP program, the TEACCH program, and another model. And that was an interesting study. They actually didn't find differences.

And I'm also aware that there -- isn't there a study that Sally Rogers is conducting, or in some other groups, looking at the difference in outcome between a discrete trial approach and a naturalistic approach? So we actually have a little progress underway here that we hadn't reflected, if I'm interpreting the objective correctly.

Dr. Croen: Yeah. I don't really understand this objective the way it's written in this one sentence. Gerry, do you have a -- can you --

Dr. Dawson: Well, I just remember that there were some people that were sort of questioning the -- you know -- that ABAs can not only have positive, but could sometimes have negative effects if it's presented in, you know, the traditional approach, and that we don't really understand yet whether ABA is better than, say, TEACCH or more natural, naturalistic early-intervention approaches.

And I remember -- as I recall, it was some of the folks, self-advocates on our team that were really pushing, you know, for the need for this kind of research.

Dr. Klin: And can I just ask you for a clarification? The thought was that, the way I read it, the impact of early diagnosis on choice of intervention. So there was a sense that the age of diagnosis would actually impact the choice of modality of treatment? Is that what people wanted to know?

[Several speakers]

Dr. Dawson: Yeah, I think that -- well, Susan, do you remember how to interpret this objective? Was it more than, you know, when you're very young and these things are kind of forced on you, so to speak, you don't have a lot of choice, right, about what you would like your own intervention to be? That this is, you know, this has an impact, perhaps, versus having a little more self-determination in terms of the type of treatments that one experiences.

Dr. Daniels: I think it's something like what Ami was saying -- about the idea that early diagnosis somehow impacts choices of intervention and then would impact outcomes. But I don't recall all -- we would have to dig back in the old transcripts to find --

Dr. Boyle: Yeah, I was going to say, maybe we need some clarity about what this is supposed to do here.

Dr. Dawson: Yeah. I think we really do, Susan, because I'm sort of guessing from memory of conversations, and that's not appropriate.

Ms. Meek: And that's all probably

contributing to the zero-dollar amount here.

[Laughter]

Dr. Dawson: Good point.

Dr. Daniels: Maybe funders had a hard time trying to match things up.

[Laughter]

The studies you mentioned -- I'm sure they're in the portfolio analysis. They're coded elsewhere. So those would probably overlap here. But we could try to get some clarity about what exactly the intention was with this objective.

Dr. Klin: We have a randomized control trial beginning at 12 months. And -- but I think that -- I think it's hard to understand the way that this is stated in those two lines. So I think that that's the challenge there.

Dr. Daniels: Okay. So maybe then we should table this until we get the old transcripts and see exactly what was said as they developed this one.

Okay. So, the next one is 1.S.E: “Conduct at least one study to determine the positive predictive value and clinical

utility, such as prediction of co-occurring conditions, family planning, of chromosomal microarray genetic testing for detecting genetic diagnoses for ASD in a clinical setting by 2012."

The recommended budget was determined to have been partially met by the Committee the last time they talked on the phone. The Committee would like an update from experts about the field about the applicability of microarray testing and whether this objective should remain a priority.

And I know on the last call, some members of the Group felt that maybe this should be lowered in its priority as maybe not being as important as some of the other things that are going on in the field.

So can some people comment about this one and what you think is going on here?

Dr. Croen: Well, I've, this is Lisa, I know that there, that you know, array CGH is sort of in guidelines and is recommended. However, the clinical utility of it is -- there's a lot of disagreement about that depending on whom you talk to and how useful

it is for families to know what the findings are, because there are so many findings that -- I mean, you can have a lot of findings. But the implication of those findings are sort of unknown at this point. So how useful is it to tell families that they have this particular de novo this or that or whatever it is?

So maybe it's not written this way, but I think research on understanding how the impact of these findings on families and providers would be useful to have that kind of research because I don't think it's really being done.

Dr. Dawson: So a couple of things: One is that I believe that in the last year, but that the American Academy moved from recommending that microarray testing be offered versus that it be conducted. So it took a step actually toward stronger recommendation for microarray testing.

And to me, that seems like if that's what the American Academy of Pediatrics is telling people to do, then we really do need to have a better understanding of how to

interpret those findings. And I think the goal behind this objective was that we really need, you know, more, databases where when we see, you know, rare mutations, for example, we understand how these map onto different phenotypes and how to interpret them.

So the work that David Ledbetter and others are doing where they're developing large databases from different clinical populations and looking at the correspondence between different kinds of findings on microarray and clinical phenotypes, I think is pretty essential. But that's just my opinion.

Dr. Klin: I can just add that -- well, one of them, I think that at this point in time, I believe that geneticists would state that microarray is just in the clinical utility. It's something that one can recommend after there is a concern about a child's development. In that way it can be helpful.

But of course, this objective here is stated as something quite different, just basically using genetic probably genomic

testing in order to identify risk. And I would love to know, what are the projects that are funded already? And just to mention there are huge -- to my knowledge -- a huge private clinical trial happening right now, but I know of one.

But I know that the service is actually being advertised as a subject direct to consumer by several private companies as well. So I think that this is really critical. I'd like to know who is funded by NIH to create that body of knowledge.

Dr. Boyle: I guess David Ledbetter. I think he has two projects there. I think I looked the last time.

Dr. Klin: Who's that?

Dr. Boyle: Yeah, David Ledbetter.

Dr. Klin: No, no, I know David well. But I've spoken to him several times, and I don't remember him doing that kind of study.

What I'd love to know is, for example, the kind of study that SynapDx is doing, what kind of results they're getting. Because there was an issue of risk communication in regard to genetics genomic testing that we

need to address in autism. And we had a recent conversation about that.

But I don't know if 300 to 500 mutations, none of which accounts for more than a very, very, very, very, very small percentages of cases. I think that if you ask, like an expert like Ed Cook, he might tell you that he doesn't see this becoming clinically relevant in the near future. But so that's why the data on this is so critical.

Dr. Dawson: So, just a couple of comments. One is that, Ami, I don't think that this objective is meant to be doing microarray testing in the general population. So that is not -- because I remember being involved in writing this objective and weighing in on it. So the purpose here was to say, in a clinical setting, for ASD where you're then -- after you have a diagnosis of ASD -- how useful is it in terms of understanding potential genetic diagnosis.

So for example, if you have a diagnosis of autism, and then you do microarray, and they find that you have a shank mutation,

right? Or they find that you have, you know, some other specific, you know, syndrome that we know about, through microarray testing, how useful is that?

And you know, I think the argument on the other flip side is that, although these, you know, show up only in a small percentage, cumulatively, they should show up in maybe 10 percent of cases that you would do microarray testing on. And some of those have real implications for medical management.

So increased risk for cancer in some cases, increased risk for seizure, so they need, you know, increased monitoring for that and things like that.

Dr. Klin: By all means, by all means. In that context, by all means. The standard of care, I think that's just as it was mentioned before, I think that the published practice guidelines recommending microarray testing as a standard care for children with those kinds of vulnerabilities.

I was just throwing out the term "positive predictive value." So that sounded to me more like a screener rather than sort

of what we just discussed.

Dr. Dawson: Yeah. No, I agree that that term --

The other thing is, SynapDx I think is looking at gene expression, right, RNA expression --

Dr. Klin: Right.

Dr. Dawson: -- as compared to, say, something that would come out of microarray.

Dr. Klin: Um-hmm.

Dr. Croen: But do you think we have any studies that are really looking at the clinical utility of doing this microarray testing? I mean, how -- you know, there are some variants that can be detected that would suggest some kind of medical management, where if you didn't know what that genetic finding was, you know, you may go down a wrong path.

But does it -- I don't know what the evidence is. It seems like there are so many findings, and each one is so rare. And we don't really know how specific those findings are -- well, not just specific. We don't really know what those findings are. We

waited till the autism, per se, in that child.

Dr. Klin: I think -- yeah. I think one of the problems is that we don't have prevalence rates. I think that until we have some kind of a birth cohort, we don't know the prevalence rate, so it's hard. But from a clinical standpoint, the clinical validity, I think, is probably obvious.

Imagine that every child who is found to have a congenital heart anomaly is micro-arrayed. So, has to, has to be. And so I see the immediately clinical validity. I think it's hard to know what's the impact on the field, given that we know so little about the prevalence rates of those mutations.

Dr. Croen: In the general population, you mean?

Dr. Klin: Yeah.

Dr. Croen: Yeah.

Dr. Daniels: And it certainly has, this is Susan, some overlap with Question 3. We just had their call this morning, and they were talking about some of those very same issues. But they're getting the point now

where around 20 percent or so of kids can be tested and have a finding, but not know exactly what the implications are. But that they are working toward that, and the field is moving forward. And they expect to have more information about that in the future.

So many some of the people from that Group might be able to comment on this as well.

Dr. Boyle: Is Dan Ledbetter coming?

Dr. Daniels: No, but we have Joe Buxbaum.

Dr. Boyle: Okay.

Dr. Klin: And Krista Martin, who works with David, would be great, too.

Dr. Daniels: So, yeah. So we will have some overlap there. All of these questions have little pockets of overlap.

Dr. Boyle: I mean, to me this Question is misplaced. And it probably should be in -- I don't know. To me it's not related to screening or diagnosis. It's almost post-diagnosis and trying to understand the prediction of co-occurring conditions.

Dr. Croen: Yes.

Dr. Klin: See, that's why I think I got, in a way, I got the wrong interpretation --

Dr. Boyle: Yeah, yeah.

Dr. Klin: -- because I saw that as a screening and diagnosis thing, which is very hot in the field. But we don't have much of an idea. It was mentioned the notion of those large databases on specific mutations. I think the problem is that we don't have that. And we have maybe the exception of very simple disorders. I think we are not going to have them for a long time.

Dr. Boyle: Yeah.

Dr. Daniels: Well, good. Well, hopefully on Friday there will be a little bit of crosstalk on that. So you can get some more information.

Dr. Boyle: Yeah. And Gerry, I mean, maybe just one last question for thinking through for Friday. I mean, given that the American Academy of Pediatrics did come out with a recommendation to do chromosomal microarray testing for all children with a diagnosis, I mean, obviously, you know, I think Lisa said this. Physicians and families

need to know what to do with the information.

I don't know if there are certain markers that they were particularly, you know, focused on. But it just does seem like a tool that's being recommended for practice, with not a lot known about what it means.

Dr. Dawson: Yeah. No, I agree. I think that the issue really is, although there are some findings that, you know, people understand, and I think feel pretty confident in terms of feedback, when you think about a general pediatrician, if they were trying to handle a case and say, you know, in a community where you don't have a specialty center, and then they did microarray testing, they would have to somehow know how to interpret this information.

And you know, it's information that changes rapidly. And so, yeah, I don't think there are really good guidelines on that. But I do think there are people thinking about this Question pretty deeply and working on those kinds of things.

Dr. Daniels: Well, let's move on to the next one. 1.S.F: “Convene a workshop to

examine the ethical, legal, and social implications of ASD research by 2011. The workshop should define possible approaches for conducting future studies of ethical, legal, and social implications of ASD research, taking into consideration how these types of issues have been approached in related medical conditions."

And so, the NIH and OARC cosponsored a workshop on this in 2011. And the workshop video is posted on the IACC Web site under "non-IACC Meetings and Events".

And the last time the group discussed that, follow-on activities may be warranted in the form of future workshops focusing on particular subtopics of interest. But what do you see happening in this field? What might be changing? What are the needs in this area?

Dr. Klin: Could you tell me who led that workshop?

Dr. Daniels: So, you mean, like who the individual school or the institutes or --

Dr. Klin: I know that there was a very successful one that was funded by Autism Speaks. But this one in particular I'm not

aware of. So would like to know which investigator led that?

Dr. Daniels: So that one was held by the NIH Autism Coordinating Committee, and OARC also cosponsored it. Alice Kau and I chaired.

Dr. Klin: Oh, you did? Um-hmm.

Dr. Daniels: In 2011, but it was right before the end of the IACC authorization. And so everything kind of went silent after that because the authorization -- well, the IACC was reauthorized, but needed to reconstitute. So it took some time before we really were able to get back together, and we were only able to give a brief update to the Committee about it.

Dr. Klin: I'm a little biased in this area, so I'll share my opinion. I think that in the field of screening and diagnosis, and I think that there will be enlightenment eventually concerning biologically based assays that will be used for screening.

I think that this is a very critical item. I think that there are major, major, major issues, major biological issues that could actually undo this research [inaudible

comment] if they are not addressed in two ways. One very seriously and thoughtfully with professional bioethicists but actually that we don't encourage research in this area. I see that there is plenty to actually research in order for us to have a better way to come up with guidelines.

I mentioned that there was a fantastic Autism Speaks workshop in this area, and Gerry was part of a leading member in that. But I believe that there is a lot of work that needs to be done. And with a recommended budget of $35,000 a year, I don't feel that this sufficiently supports it.

Dr. Dawson: Ami?

Dr. Daniels: It's supposed to be a 1-year funding to have a workshop for $35,000. The workshop ended up costing $71,000. But ASAN also did a workshop, and it would be great if I could get information about the Autism Speaks one, because I haven't heard about that one.

Go ahead.

Dr. Dawson: Well, I was just wondering, Ami, if you could elaborate just a bit on

what you -- you know, some of the -- just a few of the topics that you think would be key in terms of, you know, continuing to sort through the bioethical issues in this area.

Dr. Klin: Sure. Well, we had a discussion recently, the Baby Siblings Research Consortium, which was a fairly large number of sites doing prospective longitudinal studies of infants at risk as well as infants at low risk for autism. And there were a series of topics that we all inventoried, and we realized that needed to be addressed very thoughtfully so that, just because we can do this form of research, we should do it is not, obviously, something that we can accept.

There are many things. I think that the workshop that was done under the auspices of Autism Speaks focused a great deal on risk communication. And risk communication is a huge topic in genetics and genomics testing. But the same kinds of issues impact another thing that we've been discussing, given the fact that we are basically communicating risk to families.

And so, how to do it, when to do it, or ways of doing it so that this has, you know, the families' best interest in mind and so forth -- major, major issues.

We had tremendous health disparities in the field. Are we to develop, are we to invest a great deal of resources in resourcing kinds of solutions even knowing that this might not be widely disseminated so that we can address public health challenges more broadly? I mean, there are just a whole series.

Dr. Dawson: Right. Okay. Now, that's very, very helpful. And I do remember the conversation that we had at the Baby Sibs Research Consortium. And I think, you know, that really helped to highlight a number of issues.

[Pause]

Dr. Daniels: Anyone else have any thoughts about this?

[Pause]

All right. So then, let's move on then to 1.L.A: “Identify behavioral and biological markers that separately, or in combination,

accurately identify, before the age of 2, one or more subtypes of children at risk for developing ASD, and evaluate whether these risk markers or profiles can improve early identification through heightened developmental monitoring and screening by 2014."

So Committee members who met last time thought that the recommended funding for this objective has been met and that there are more than 40 projects that have been supported in this area and that identifying reliable early biomarkers has been challenging, but some progress has been made. And I know some people on the call here have more knowledge about that.

So what do you feel is happening in the field of biomarkers? What are the remaining needs and challenges in the field?

Dr. Croen: This is Lisa. I think there have been many studies that are funded looking at trying to identify biologic markers. They're not all early-biologic markers. I think a lot of the studies are looking at kids or even adults or adolescents

who are already diagnosed and looking for various biological or behavioral markers of the disorder.

I don't know how applicable those will be for early identification and diagnosis, the way this is stated, before the age of 2.

And then, you know, so I think the work is -- there's -- a lot of work is going on. But how they can -- the second part that's written in red here, how they can improve early identification, I don't think that work -- I mean, there are some studies going on, but not a whole lot that have a lot of application, I think. We're not ready for prime-time thing. Okay, we've got a really reliable biomarker here -- behavioral marker for early autism.

Dr. Boyle: This is Coleen. I would agree with what Lisa just said. Lots of promising work, lots of activity, but when you actually think about trying to use these either in the population or a clinical context, I mean, again there's -- we're not there. We're not there yet.

Dr. Croen: Yeah. And the other point

about that, I think, is there's a lot of very interesting research going on. But the types of markers and the technologies that people are using -- I mean, the application, again, in community settings for identifying kids early -- I think a lot of the studies are not translatable to actual practice.

They may be something that can be done in a research setting, in an academic center doing research. But in terms of community settings and clinical -- you know, actually where you're trying to really identify kids early for clinical reasons, they don't seem to be -- may not be too applicable.

Dr. Klin: I think some of the biomarker workshops that I've been to, one of the main concerns that I would put out there is that there is great research going on. And there are some great even quantitative markers. They have been shown to separate populations, but not necessarily individuals. And I think that we need to make sure that we're talking about something not unlike a medical test that is going to separate individuals, so that we have acceptable levels of

sensitivity, specificity, and so forth.

Dr. Dawson: Yeah. I think in that regard, you know, most of the work that has been done to date is really comparing, you know, kids who develop autism versus not, often in a high-risk population but sometimes just in a case control. And there's very, very little, if any, work that has validated a marker in the general population or that could be used in any kind of clinical setting as a frontline biomarker.

I don't even know if we're close, frankly, to that. So I don't know how other people feel about that.

And then the other issue is that, ideally, when we talk about subtypes in this, you're linking a biomarker to underlying biology to treatment. And I also don't think that we have, you know, good biomarkers that, you know, can predict response to different treatments or really can signal, you know, biological subtypes that might, you know, map onto signaling pathways. I really think there's a lot of work to be done here.

Dr. Klin: I wonder if we can contact our

colleagues at the FDA and ask them if there is any clinical trial right now going on. Because I'd be surprised if there was.

[Pause]

Dr. Daniels: So what needs to happen to address this area better?

Dr. Dawson: Well, I would recommend that we do need research that really is trying to link the biomarkers to subtypes and particularly to responses to different kind of treatments, whether it's behavioral or biological. And then I think, also, you know, studying -- so, for example, if there is a biomarker that is found in a high-risk infant design or perhaps in the premature infant design, so it's still a high-risk infant design that is promising; those need to be validated in the general population if the goal is to use them eventually in that context.

Or it can better understand in what context can they be used with some validity. Is it only with a child who already has a risk like an older sibling, for example?

Dr. Klin: Um-hmm. I would second that --

I think there are two aspects that I would love to see incentivized. One is lab-based biomarkers bridge to translation, something that might have been developed within the context of a lab, but something that can one day translate into a device that could be broadly deployed, meaning that it needs to be cost effective and so forth. So the translational part of biomarker research is one.

And the other one is really the applicability in general setting, a setting in which a biomarker is typically used in other conditions -- general population.

[Pause]

Dr. Daniels: Good. Anything else?

All right. Let's move on to 1.L.B: “Develop at least five measures of behavioral and/or biological heterogeneity in children or adults with ASD, beyond variation in intellectual disability, that clearly relate to etiology and risk, treatment response, and/or outcome by 2015.”

The group that met previously thought the budget for this objective was partially

met. And there were several projects, more than 50 projects, supported in this area. And while the behavioral and/or biological heterogeneity were well covered through these projects, that there were still gaps relating to etiology and risk, treatment response, and/or outcomes.

So what do you think is the state of the field here? And what are the challenges and needs?

[Pause]

Dr. Croen: Well, I think I would agree with the conclusion of the last group saying that the gaps still exist and relate these to etiology and risk and treatment response and outcomes. I mean, you know, a lot of money has been spent on this. And people are looking for markers of or measures of heterogeneity and subtyping, if that's what this is relating to.

I don't think we're really there yet in being able to, say, have any definitive marker, measures that say, okay, we've got a measure of this type of -- this subtype of autism or that subtype. And certainly, we

don't have anything, I don't think, that links whatever markers there may be to etiology or risk or treatment outcomes.

So I think there's a lot of work that still needs to be done in this, for this objective.

Dr. Boyle: And I guess I said this on the last call -- is that, you know -- there may be very different subtypes relating to etiology and then relating to, you know, treatment and impact of treatment. So I mean, those are not necessarily the same profiles or markers.

Dr. Croen: Right.

Dr. Dawson: So I would be interested in what people think about whether this Question should be -- or objective should be -- broadened to incorporate the new sort of RDoC's perspective, meaning that, you know, would it be helpful to expand some of these dimensional characteristics, not only of core symptoms, but other RDoC-like dimensions, you know, executive function, fear circuitry, et cetera? And to really understand these as they might go across different disorders and

linking them to underlying biological systems, as is the intention of an RDoC's perspective.

It's probably not a good idea. I'm just throwing it out there.

Dr. Croen: I'm trying to understand what you're saying, Gerry. I don't know if I --

Dr. Dawson: So NIMH has -- are you aware of the RDoC initiative?

Dr. Croen: Yeah, somewhat. Um-hmm.

Dr. Dawson: So I guess, when you think about these continuous dimensions, it's important to think about how they might, you know, go across different disorders, whether you're talking about repetitive behaviors, social reciprocity -- for example, social communication disorder -- or even, you know, other conditions where social reciprocity might be affected.

I just think that there -- I think that the RDoC perspective has some real value. And this particular objective, I think, touches on it, which is, you know, not thinking of these things as all or none, and understanding how they might merge into the

normal population or merge into other conditions.

So again, we don't have to grapple with that. But I do think it's an important area of research in autism that hasn't really been well understood.

[Pause]

Dr. Daniels: Any comments from other members of the Group?

Gerry, your comments may also apply somewhat to the next objective, which is, “Identify and develop measures to assess at least three ‘continuous dimensions,’ such as social reciprocity, communication disorders, and repetitive and restrictive behaviors, of ASD symptoms and severity that can be used by practitioners and/or families to assess response to intervention for people with ASD across the lifespan by 2016.”

And the last time the Group met, they felt that this objective was partially met in terms of budget and projects and that basic aspects of the research were underway, but more work is needed for the studies to be applied for use by practitioners and/or

families.

Dr. Croen: So is this objective intended to mean developing outcome measures?

Dr. Daniels: Which one?

Dr. Croen: The one you just read, yeah -- so developing, you know, sort of some outcome measure that can be used in studies to look at effects of intervention and treatment? Is that what this is getting at?

[Pause]

That can be used by practitioners and families to assess response to intervention. So --

Dr. Klin: I would say two possibilities. One of them is that those measures are predictive, basically prescriptive, or develop measures of outcomes. So I'm not sure which one of the two, or both.

Dr. Dawson: Yeah. I think when this was written -- and by the way, I truly apologize. I was focusing on the last one. Maybe I was just hoping we were already there.

[Laughter]

But anyway, yeah. This was written, I think, with the idea of, you know, being able

to use this in a wide range of research, including outcome research, like clinical trials, for example, if not intervention.

Dr. Croen: Right.

Dr. Boyle: Yes. So this one, Gerry, I agree is probably more appropriate for the RDoC-related perspective. Although I was trying to think through the last one as well.

[Laughter]

Dr. Klin: I'm a little concerned. We're talking about 1.L.B, right?

Dr. Boyle: 1.L.C.

Dr. Klin: Oh, 1.L.C.

Dr. Daniels: They're kind of similar.

Dr. Klin: Yeah. So quite a bit of money has been invested.

Dr. Croen: Yes. So what I -- I guess, what kind of -- what has been done in this area?

Dr. Klin: I think that if you take some of certainly the drug clinical trials, if major advances have been happening in this area, they haven't quite reached those trials yet. Because I would be very frustrated. I think we have terrible, terrible, terrible

treatment outcome – terrible to say.

Dr. Dawson: Yeah. I agree. And, you know, Autism Speaks sponsored this full review of outcome measures in the area of social reciprocity, anxiety, and repetitive/restrictive behaviors. And all three of those comprehensive reviews -- and we evaluated each one of those and developed consensus about whether they're, you know, appropriate for clinical trials, what needs to be done to make them better, et cetera.

Anyway, all three of those papers are in press. And I can tell you that, you know, the general conclusion is that we really don't have a lot of good measures. These things that are sensitive to change and valid and can be used with -- you know, that aren't super burdensome that could be used in a large clinical trial and so forth. But it sounds like there's work underway.

Dr. Klin: Yeah. Gerry, I can't remember if you're part of the -- I think, or Coleen. Are you part of the Foundation for NIH biomarker task force?

Dr. Boyle: No, I'm not.

[inaudible comment]

Dr. Klin: Yeah? Somebody else?

Dr. Boyle: Gerry, are you?

Dr. Dawson: No. I was part of The Biomarkers Consortium meetings early on, but I'm not part of the task force, no.

Dr. Klin: It's just because I was just wondering, that task force, or whatever it is -- so it meets every 6 months or 8 months or so. And I think the purpose, though, is to develop -- is to somehow to encourage the development of quantitative methods for treatment outcome in the context of the risky investment from pharmaceutical companies in developing new compounds.

And one of the frustrating parts of those meetings is there is so little to go around. And yet there is so much need, so much need.

[Pause]

Dr. Daniels: So do you have thoughts about what are the next steps that need to be taken in this area? Obviously, some investment has been put in already. But what is holding this back from moving forward

more?

Dr. Boyle: Susan, just let me ask a question. Do we have -- I'm still trying to pull this Question up, or part of it -- Do we have measures to assess the continuous dimensions of autism symptoms in their severity?

Dr. Daniels: There are a number of funded projects to look for those or to develop measures.

Dr. Boyle: And I'm looking through them as we're talking.

Dr. Dawson: So the measures we have are things like the social withdrawal subscale of the aberrant behavior and of checklist, or the PDD behavior inventory, or the -- you know, these kinds of measures, which -- they're using clinical trials that have still been, you know, somewhat low. So they're not well validated enough that the pharmaceutical companies feel real confident in them?

You know, think about the arbaclophen trial and how hard it was. You know, they actually got a signal on one of their social measures. But they just didn't choose the

right one. Because they chose social withdrawal subscale because that's the one that showed up in the last trial that they did, and it didn't show up in the next one. So you know, it's very hard, I think. And it's

-- you know, the subscale, the ABC wasn't measured or wasn't developed to assess treatment response in a pharmaceutical-type trial, either. So it's pretty sorry state, I would say.

Dr. Boyle: Okay.

Dr. Klin: I think one of the concerns that I have about this field in general is the level of quantification. I think that some of those checklists, the clinical rating scales, they tend to have very few levels of -- in their scale. And I think that when you treat the condition, a chronic condition as autism for short periods of time, you know, using those very blunt kind of ways of quantifying social behavior, I believe that it's going to be hard.

So if I were to wish for a change, it would be to test, once again, performance-

based measures in the context of a treatment protocol that is known to benefit children. And the real question is the extent to which one can use something that will quantify change.

I haven't seen anything like that at all. I'm worried that focusing on the checklist, it's going to be hard, that we're going to be complaining about treatment outcome tools forever and ever.

Dr. Dawson: Yeah, I agree with you, Ami.

[Pause]

Dr. Daniels: Any thoughts about this one?

Dr. Klin: I know. Spiritually, I'd love for this document eventually to become, you know, talking about the aspirational goals. I think that we need to demand more from ourselves and from the field. And major areas of need are quantification, quantification. And I would like to see more and more incentives for those things to happen.

Dr. Dawson: I guess the other thing is looking at the projects that are listed here -- I hope I'm in the right one -- Is this --

Dr. Boyle: This is L.C, 1.L.C.

Dr. Dawson: Yeah, 1.L.C, okay. Yeah. For example, we have –

Dr. Boyle: What year are you looking at?

Dr. Dawson: I'm looking at the 22 projects that are funded. If you click on that link, you can actually see the projects.
Dr. Croen: From one year, from 2010?

Dr. Boyle: All different years, Gerry.

Dr. Dawson: Oh, I'm looking at --

Dr. Croen: 2010?

Dr. Dawson: 2010, which is --

Dr. Boyle: 2010. Yeah. Okay, we're there with you.

Dr. Dawson: Okay. So you know, I just -- I can't imagine that most of these were developed with the idea of developing a sensitive assay for measuring quantitative change in a clinical trial.

Dr. Boyle: Yeah.

Dr. Croen: Yeah. That's my feeling, too. That's what I -- and you look at the more recent projects. I think this is the issue across all of these different objectives, is that the projects that are linked to the

objectives, it's hard to really see how they're addressing those objectives directly.

Dr. Boyle: Right.

Dr. Croen: And in the sense of, you know -- yes, there's been a lot of funding put toward things that might eventually lead to reaching the objective, but has the objective been satisfied or met yet? And I think the answer to most of these is no.

Gerry, what your comment was when we talked about the very first objective; you know, you can't say right now that we've got some tools that -- I don't think. I mean, you're more the expert on this for sure -- that can measure continuous dimensions that could be used effectively in measuring outcomes of interventions of any kind, pharmaceutical or behavioral, whatever the treatment approach is.

[Pause]

Dr. Daniels: Any other comments?

Dr. Klin: Can I ask you a more general question? I'm sorry if I'm -- I should have that discussion initially. It seems like you guys have a list of older funded projects per

item?

Dr. Boyle: Yeah.

Dr. Daniels: So what you have with you is -- you have the Cumulative Funding Table that I sent out. And in order not to burden you with too much documentation, I didn't resend the documents from the past phone call. There were a number of documents there.

So the past phone call -- those ones are posted on our Web site. But on the Cumulative Funding document, if you click on the listing of projects for each objective from 2008 through 2010, you can get a project list, because those are uploaded in our Web tool.

For 2011 and '12, I sent out to the people that were on the previous phone call an actual Excel spreadsheet listing of all the projects because those aren't live in the Web tools yet.

Dr. Klin: Oh. I got it. This is wonderful. This is wonderful.

Dr. Daniels: So the 2011 and 2012 documents, they're on the Web as well, but they're not live in the Web tool, so they're not interactive.

They're just static documents, but at least you can easily look at 2010 just by clicking on the --

Dr. Klin: I got it. Thank you.

Dr. Boyle: That tool is great, by the way, Susan.

Dr. Dawson: Yeah. It's an amazing amount of work, I'm sure.

Dr. Daniels: I'm glad to hear that it's useful.

Dr. Boyle: Yeah. It's just, it is, as Lisa was just saying -- and I know we talked about this before. It's hard to figure out which category to put some of these in. A lot of them will go into the “Other.”

Dr. Daniels: And something I should point out. So, the last line in this table is not specific to any objective, or “Other.” And on the previous phone calls, we've been talking with other Committee members and external participants that perhaps we need to change the name of this from "Other" to something that's a little bit more descriptive, like "Core Activities" or something.

Because these projects in “Other” are really kind of the core-based funding that is not related to the objectives. The objectives were addressing gap areas. But there was still a body of funding that existed before the Plan came into action. And so all of those kinds of projects that aren't addressing the specific gap areas identified by the Committee are in that category. And unfortunately, it has a non-descriptive name like "Other." So we may talk with the Committee about changing it.

Dr. Croen: But all of the projects listed in the “Other” category now were coded to this Question Number 1, which was Screening and Diagnosis; is that correct?

Dr. Daniels: Yes.

Dr. Croen: And what you said before, Susan, is that every project that's in the body of -- I mean, that's been funded by NIH or other foundations that have to do with autism have been coded to just one question, and then within one question, one objective?

Dr. Daniels: That's right. And so, if they didn't fit in any of the objectives,

they went to “Other.”

[Pause]

And from the last call, I can redistribute the documents from the last call that have a lot more detail about the portfolio. But to keep things simple on this call, I didn't send you all that information. But we have more of a breakdown in terms of what's been funded in each question.

Dr. Boyle: So, Gerry, you were going to make a point and I interrupted you. I apologize.

Dr. Dawson: No, I think I already made it.

Dr. Boyle: You already made it? Oh – I apologize.

Dr. Dawson: Yeah.

Dr. Boyle: It's getting late in the hours.

[Laughter]

Dr. Dawson: It wasn't very profound, but I did make it.

Dr. Boyle: Okay.

Dr. Dawson: Yeah. I just worry that this is one where if to meet this objective, you

really need projects that are specifically trying to tackle that problem. And I don't think that some of the projects listed, although they're very important and helpful in reaching the goal, are not targeted specifically on that goal.

Dr. Klin: I could not -- I cannot agree more strongly. I think that, going back to the RFA that we talked about that focused on parent engagement, I just say that that's one of the more precisely written RFAs that I've seen in a long time. I think that the way that RFA was written was very precise.

The requirements really encourage people to do what the field needs, too. And so I think that what Gerry just mentioned, if that was actually enshrined in a nice RFA, it would be terrific. I know that we're not talking about that.

Dr. Daniels: Right, right. And in the first year -- so on the Cumulative Funding Table, you'll see 2008, which was the year before the Plan was actually launched. And that served as a baseline. And in that first year, we were taking a more strict approach

to coding. And so a lot of projects ended up in the “Other” category.

But the Committee feedback we got was that they wanted to see us try to find where projects might be supporting the general ideas of the goal, even if they weren't extremely specific for what was written.

And so you'll see, if you look over time, you'll see that there are fewer items that end up in the “Other” category, because where possible, we and the funders worked to try to make them -- you know -- to link them up with some of these objectives, if they had some relevance.

But just to give you that background. If the overall approach had been to be extremely strict to all of the different words in these objectives, we probably would have had pretty much all the projects in “Other,” which wouldn't have been too informative.

[Pause]

So, is it okay for us to move on to the last part of this call, which would be talking about the aspirational goal? I want to hear what you all have to say about the

progress that's been made to date on the aspirational goal for this Question, which is, “Children at risk for ASD will be identified through reliable methods before ASD behavioral characteristics fully manifest.”

So this is, you know, the ideal goal that the Committee wants to strive for in this part of the Strategic Plan. So how do you think we're doing here? And where are we right now? Where would you like to see us be going? Are there things, steps that could be taken, that would move us along more quickly?

Ms. Meek: I'd just offer that Ami's work gets us a lot closer.

Dr. Klin: I appreciate that comment. I think that there is a need for mechanisms that allow us to get from a small scale to large scale, from lab-based to community-based. I think that one had to set up, do a lot of sampling and a lot of data points, but I think that if there were a mechanism out there that awarded those programs out there that have something that can be translated, it would be great.

Because the bottom line is that aspirationally ultimately, we would like to have a test for this condition, a real test, not unlike in other branches of medicine. So just to give you a sense, we were able to set up -- translate or take our lab and make it into -- a small-footprint device that can be deployed in community health centers. But in order to test its validity in a community center, we have to fund our own clinical trial, which is a fairly large enterprise.

Dr. Daniels: For those who are on the phone, can you just briefly mention what that is, for those who might not be familiar?

Dr. Klin: Well, we conducted a study with infants at risk. We took 10 measures before the age of 24 months, 6 measures before the age of 6 months. And we found some quantitative -- well, we created a quantitative assay based on eye-tracking technology to quantify eye fixation decline, as well as some other measures that appeared to be predictive of classification for children later diagnosed with autism at the age of 24 to 36 months and also predictive of

level of disability.

It's a good study, but it's a small study. And so it needs to be replicated in a much larger sample. But most importantly, it's totally -- in order for us to aim at a large-sample replication, we decided that we're going to try to translate what is a lab into something that might be potentially, ultimately be deployed in a primary-care physician's office as part of a well-baby checkup.

And so we had to invest in creating that prototype. That prototype has been developed. And we created a -- we met with the FDA, and we created the clinical trial design we're submitting now to FDA for approval. And we're planning to conduct a clinical trial in 2014 in several sites around the country.

But the only reason why we can do that is because we had to fund-raise. It's not built as an NIH clinical trial. It's basically built as a clinical trial carried out by a private company.

Dr. Dawson: So let me make just a comment here. First of all, I really applaud

Ami's work, and I even put that in *The New York Times*, so it's true. But I would say that we still -- well, first of all, there have been a number of discoveries over the last year, too, in terms of early markers. I think Ami's stands out as being particularly elegant and also quantitative and emerging very early.

But there really have been other -- you know, motor impairments, such as reaching and posture, difficulties in disengagement of attention, electrophysiological measures such as neural sensitivity to eye gaze, alpha A symmetry, differential patterns of functional connectivity based on mirrors. I could go on -- and all, all the different characteristics now that have been shown up in high-risk infants that go on to predict which children develop autism.

And I guess what I would say is that really now we need to understand these in other populations. In the general population, in other high-risk populations, you know, such a premature infants or infants that might have a genetic condition, such as

fragile X or TSC (tuberous sclerosis) that has high risk for autism.

So I still think there's a lot of work to be done to understand how these would really operate in the general population. Because when you're just comparing “I have it” or “I don't”, you know, in a high-risk population, that's a very, very important first step. But they just may not work the same way in the general population.

Dr. Klin: I could not agree more strongly. And I think that it would be important to have mechanisms that would basically pit those different methods, I think on the basis of two things.

One of them -- is this a group result, or does this have individual -- does it have meaning for an individual child? I think that that's something that separates some of the more advanced work from the work that is not quite advanced.

And secondly, how does that fare in the real-life situation where children of all kinds of shapes and colors are seen for a whole range of developmental vulnerabilities?

I think that those two criteria are critical for us to know whether or not we will one day be able to move from a lab to a community.

[Pause]

Dr. Daniels: Other thoughts?

Dr. Boyle: This is Coleen. I mean, I think that the aspirational goals should remain. I mean, I think it's, you know, the thing that keeps us driving forward. But I agree with the conversation that, you know, we have bits and pieces of work that are going on to perhaps get us there.

Dr. Croen: Yeah. And I agree as well with everything that was said. I guess I want to underscore this issue of translatability and application in the community. I think it's great to have these studies measuring all different kinds of things that might be a predictive test, but how useful are those in the real world, you know? How can we apply those in the real-world settings where kids are coming in for well-child care and where you really want to identify kids at risk very early?

Dr. Boyle: I mean, I relate to this. I

do a lot of work in the newborn-screening worlds. And you've just added screening for pulse ox to identify children with severe congenital heart disease. You know, it's a simple easy test that's done, you know, once or twice in the newborn period. Will we ever get to that point with autism? Or some of the autisms?

Dr. Klin: Yeah. I think that one thing that we do -- I imagine that people do in cardiology is to measure the disease itself. And so you have a screen, and you're measuring the disease or the early signs of a disease.

I think that what might happen in autism is not a screening method that is going to measure the disease itself, if the disease, whatever we call it -- a syndrome, a learning difference -- is only going to be visible in the second year of life and is going to be reliably diagnosed later.

I think that the notion of measuring for deviation of trajectories in key aspects of development might be what we're looking for. And that might end up being a very broad-

based screener for developmental vulnerabilities. So I would take that, Coleen, anytime.

Dr. Boyle: Yeah. Yeah.

Dr. Daniels: Any other items? You still have about 5 minutes. Any other items that you think would be on your wish list to get us to the point of being able to reach this aspirational goal, without going into all the minute details that might be in the objectives?

Dr. Klin: I probably would go back to something that we discussed before. That our social, cultural, ethical reality-based obstacles, that even in an ideal world in which we had the very best screener or the very best diagnostic device or tool or methods, that we will have to conquer in order to make those advances relevant to the community.

And so, an aspirational goal would be for us to, I think, to somehow do away with the health disparities that we currently have.

[Pause]

It's probably part of what you just said.

Dr. Daniels: Any final thoughts?

Dr. Croen: I don't have any more thoughts about this, but I have a question about Friday's meeting and how that will -- are we going to be getting something from you about that?

Dr. Daniels: Yeah. I'll send out an email to all of you to prepare you for Friday. We'll have about 50 minutes per question.

But we're hoping that, with the group of experts that we've invited that you'll be able to comment on multiple areas of the Strategic Plan, as most of you have fairly broad areas that you are familiar with and have expertise in. And so we hope that you'll feel free to share across the entire Strategic Plan and not just on the area that you were volunteering for, for these calls.

So we hope that there will be a little bit more cross-pollination at that meeting. And we will provide you with some instructions. But our time per question is

fairly limited. So the day will go. We have already posted an agenda on the Web site. I'll be sending that to all of you in an attachment.

But we will have a 50-minute session for each of the questions. And then we will have a working lunch, where we're going to get box lunches that everyone will have to pay for, because the Government can't provide that, so that we can efficiently get through the rest of the afternoon.

And we will have a public comment session in the middle of the meeting.

And at the end, we will have a wrap-up session before we adjourn at 5 o'clock.

Dr. Dawson: Susan, I have a question.

Dr. Daniels: Sure.

Dr. Dawson: The notes that I took on our call, are we -- would it be helpful for me to send it to this Group so that we have them? Or is that not allowed? Or what are your thoughts on that?

Dr. Daniels: Sure. If you have your notes prepared and you want to circulate them, you can send them to me and I can send

them out to the Group with other materials.

Dr. Dawson: Okay, great.

Dr. Daniels: On our end, we have a number of sets that we're preparing of materials. And so, we unfortunately, don't have such a quick turnaround.

Dr. Klin: I would like to thank everybody. Sorry, I need to run. But it's a real pleasure being part of this Group. Thank you so much.

Dr. Daniels: Thank you. Thank you all for your participation.

Dr. Dawson: Good-bye, everyone.

Dr. Boyle: See you.

Dr. Daniels: Thank you.

Dr. Croen: Good-bye.

Dr. Daniels: Good-bye.

(Whereupon, the Question 1 Planning Group conference call was adjourned.)