U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

2013 IACC STRATEGIC PLAN UPDATE WORKSHOP

FRIDAY, NOVEMBER 15, 2013

The Committee convened in Wilson Hall, Building 1, 1 Center Drive, Bethesda, Maryland, at 8:33 a.m., Thomas Insel, Chair, presiding.

PARTICIPANTS:

THOMAS INSEL, M.D., *Chair*, IACC, National Institute of Mental Health (NIMH)

SUSAN DANIELS, Ph.D., *Executive Secretary*, IACC, Office of Autism Research Coordination (OARC), (NIMH)

IDIL ABDULL, Somali-American Autism Foundation

ANSHU BATRA, M.D., Our Special Kids (attended by phone)

SILVANA BORGES, M.D., U.S. Food and Drug Administration (FDA) (attended by phone) (representing Tiffany Farchione, M.D.)

COLEEN BOYLE, Ph.D., Ph.D., M.S. Hyg., Centers for Disease Control and Prevention (CDC)

MATTHEW CAREY, Ph.D., Left Brain Right Brain

GERALDINE DAWSON, Ph.D., Duke University (attended by phone)

ALICE KAU, Ph.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (representing Alan Guttmacher, M.D.)

PARTICIPANTS (continued):

LAURA KAVANAGH, M.P.P., Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA) (attended by phone)

WALTER KOROSHETZ, M.D., National Institute of Neurological Disorders and Stroke (NINDS)

CINDY LAWLER, Ph.D., National Institute of Environmental Health Sciences (NIEHS) (representing Linda Birnbaum, Ph.D.)

DAVID MANDELL, Sc.D., University of Pennsylvania (attended by phone)

STAN NIU, Ph.D., U.S. Department of Defense (DoD) (representing Donna Kimbark, Ph.D.)

JOHN O'BRIEN, M.A., Centers for Medicare & Medicaid Services (CMS) (attended by phone)

LYN REDWOOD, R.N., M.S.N. Coalition for SafeMinds

SCOTT ROBERTSON, Ph.D., Autistic Self Advocacy Network (ASAN)

JOHN ROBISON, Author, College of William and Mary

ALISON SINGER, M.B.A., Autism Science Foundation (ASF)

LARRY WEXLER, Ed.D., U.S. Department of Education (ED)(representing Acting Asst. Secretary Michael Yudin) (attended by phone)

BALDWIN/BUCK WONG, National Institute on Deafness and Other Communication Disorders (NIDCD) (representing James Battey, Ph.D.)

EXTERNAL PARTICIPANTS:

SCOTT BADESCH, Autism Society of America
(attended by phone)

BRIAN BOYD, Ph.D., The University of North Carolina at Chapel Hill

JOSEPH BUXBAUM, Ph.D., M.Sc., Icahn School of Medicine at Mount Sinai
(attended by phone)

NANCY CHEAK-ZAMORA, Ph.D., M.A., University of Missouri (attended by phone)

JULIE DANIELS, Ph.D., M.P.H., University of North Carolina at Chapel Hill

MAUREEN DURKIN, Ph.D., Dr.P.H., M.P.H., University of Wisconsin-Madison
(attended by phone)

DANIELLE FALLIN, Ph.D., Johns Hopkins University (attended by phone)

DAN HALL, M.B.A., National Database on Autism Research (NDAR), (NIMH)
(attended by phone)

IRVA HERTZ-PICCIOTTO, Ph.D., M.P.H., University of California, Davis
(attended by phone)

AMI KLIN, Ph.D., Marcus Autism Center, Department of Pediatrics, School of Medicine, Emory University
(attended by phone)

PAUL LAW, M.D., M.P.H., Kennedy Krieger Institute

THOMAS LEHNER, Ph.D., M.P.H., National Institute of Mental Health (NIMH)

SHANTEL MEEK, M.S., Administration for Children and Families (ACF)

EXTERNAL PARTICIPANTS (continued):

NANCY MINSHEW, M.D., University of Pittsburgh

CARLOS PARDO-VILLAMIZAR, M.D., Johns Hopkins University

KEVIN PELPHREY, Ph.D., Yale University (attended by phone)

JAMES PERRIN, M.D., Harvard University (attended by phone)

KAREN PIERCE, Ph.D., University of California, San Diego

PAUL SHATTUCK, Ph.D., Drexel University

AUBYN STAHMER, Ph.D., M.A., Rady Children's Hospital and University of California, San Diego

JEREMY VEENSTRA-VANDERWEELE, M.D., Vanderbilt University

DENNIS WALL, Ph.D., Harvard University (attended by phone)

PAUL WANG, M.D., Autism Speaks

ZACHARY WARREN, Ph.D., Vanderbilt University

AMY WETHERBY, Ph.D., CCC-SLP, Florida State University

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PROCEEDINGS:

Dr. Thomas Insel: Good morning. This is Tom Insel in Wilson Hall at NIH, and we're just having everybody sit down.

Thanks to those of you who are joining us on the phone. And I think we've got enough of a group here to get started, and maybe the best way to do that -- because this is a workshop that involves not only IACC members but some experts from outside -- is we'll go around and do a quick introduction.

And if we could just have each person say who they are and where they're from and what area they represent or which question they worked on, that would be great. And then we'll go to those on the phone as well so that those of you who are on the phone can introduce yourselves.

I'll start. I'm Tom Insel.

Operator: Excuse me. This is the operator.

Dr. Insel: Yeah?

Operator: I'm sure you know today's

conference is being recorded. Would you like that to be started?

Dr. Insel: Please begin.

Operator: Okay. It'll be just one moment. You're going to hear music momentarily, and I will do an introduction. It will be just one moment.

Dr. Insel: Thank you.

Operator: Welcome, and thank you for standing by. I'd like to inform all participants that today's conference is now being recorded. If there are any objections, you may disconnect.

Thank you. You may begin.

Dr. Insel: Thank you. And welcome to the Strategic Plan Update Workshop for the IACC. I'm Tom Insel, chairman of the IACC. And Susan Daniels, adjacent to me here, will be managing much of the day's discussion, but I wanted to get us started. We're going to do a quick round of introductions, and we'll start to the empty chair to my left is Walter Koroshetz. He and I have just come off of

another large meeting that he is still, I think, part of. So he'll probably be here momentarily, and we'll just keep going around.

Dr. Paul Wang: Good morning. My name is Paul Wang. I'm a developmental behavioral pediatrician. For the last 5 years, I worked at Seaside Therapeutics in drug development for fragile X syndrome and autism. A month ago, I joined Autism Speaks as head of medical research.

Mr. John Robison: I'm John Elder Robison. I'm neurodiversity scholar and resident at the College of William and Mary.

Dr. Matthew Carey: I'm Matt Carey, the parent of a great little 10-year-old, and I was working on Question 3 this time.

Dr. Catherine Rice: Hi. I'm Cathy Rice, a behavioral scientist with the Centers for Disease Control and Prevention, and I was working on Questions 5, 6, and 7.

Dr. Insel: So just to clarify as well, so John is part of the IACC, and Matt is part

of the IACC, and Cathy sometimes as well.

Dr. Karen Pierce: Hi. I'm Karen Pierce, and I'm associate professor at UCSD, and I work on diagnosis, screening, and also brain imaging. And I helped with Question 1.

Dr. Jeremy Veenstra-Vanderweele: Hi. I'm Jeremy Veenstra-Vanderweele, a child psychiatrist in molecular neuroscience at Vanderbilt.

Dr. Thomas Lehner: Hi. I'm Thomas Lehner. I'm a geneticist. I'm from the NIMH.

Ms. Lyn Redwood: Hi. Lyn Redwood. I'm director of the Coalition for SafeMinds. I have a 19-year-old son who is -- has just started his second year of college. And I'm a member of the IACC.

Dr. Julie Daniels: Hi. I'm Julie Daniels. I'm an epidemiologist at UNC.

Dr. Nancy Minshew: Hi. Nancy Minshew at the University of Pittsburgh. I'm a child neurologist and worked on the cognitive and brain basis of autism and now on interventions.

Mr. Buck Wong: Good morning. I'm Buck Wong with the National Institute on Deafness and Other Communication Disorders.

Dr. Stan Niu: Good morning. My name is Stan Niu. I'm the science officer at the DoD Autism Research Program. I'm here representing the program manager, Donna Kimbark.

Dr. Cindy Lawler: Cindy Lawler at the National Institute of Environmental Health Sciences, here representing Linda Birnbaum, who's a member of the IACC.

Dr. Scott Robertson: I'm Scott Michael Robertson. I'm in -- sorry, I can't get my words this morning. I'm an autistic adult, cofounder and vice chair of development of the Autistic Self Advocacy Network. And I'm an IACC member, and I worked on Questions -- been working on Questions 5 and 6.

Dr. Insel: And just an editorial comment here, you're now Dr. Robertson, we understand? Congratulations.

Dr. Robertson: Yeah, I just -- I

recently defended my Ph.D. So I'm now Dr. Robertson. Thank you, Dr. Insel.

[Applause]

Ms. Idil Abdull: Hi, everyone. My name is Idil Abdull. I have a son with autism who is 11 years old. I'm a member of the IACC, and I worked on Questions 4, 5, and 6.

Dr. Amy Wetherby: Good morning. I'm Amy Wetherby. I'm a professor at Florida State University in the College of Medicine, and I direct the Autism Institute there. And my research focus is on early detection and early intervention.

Dr. Brian Boyd: I'm Brian Boyd. I'm assistant professor at UNC-Chapel Hill. I conduct behavioral intervention research, and I worked on Questions 5 and 6.

Dr. Carlos Pardo-Villamizar: Hi. I'm Carlos Pardo. I'm a clinical neurologist and neuropathologist. As a clinician, I work in neuroimmunology and infectious disorders. As a scientist, I worked in neuroglia and brain development.

Ms. Alison Singer: Good morning. I'm Alison Singer. I'm the cofounder and president of the Autism Science Foundation. I am the mother of a 16-year-old daughter with autism, and I also have an older brother with autism. I'm a member of the IACC, and I worked on Questions 2, 5, 6, and 7.

Dr. Paul Law: Hi. I'm Paul Law. I'm the father of a 20-year-old with autism. And I've been involved in building research infrastructure for autism since '96, working on ISAAC with Cure Autism Now. Now it's been folded into Autism Speaks. And was involved in the early days of NDAR and, more recently, have been involved at Kennedy Krieger with the development of the IAN project. Thanks.

Dr. Coleen Boyle: Good morning. I'm Coleen Boyle. I'm with the Centers for Disease Control and Prevention. I am a member of the IACC, and I worked on Question 1.

Dr. Aubyn Stahmer: Hi. I'm Aubyn Stahmer from UC-San Diego and Rady Children's Hospital, and my research is in the area of

interventions and moving evidence-based practice to community settings.

Dr. Zachary Warren: I'm Zach Warren. I'm a clinical psychologist at Vanderbilt University, working in early detection and intervention.

Dr. Alice Kau: I'm Alice Kau, a program staff from Eunice Kennedy Shriver National Institute of Child Health and Human Development. I'm representing Dr. Guttmacher today, who is a member of IACC, and he's on official travel today and couldn't be here.

Dr. Susan Daniels: Hi. I'm Dr. Susan Daniels. I am the acting director of the Office of Autism Research Coordination, which is the office that manages the IACC.

Welcome to everyone.

Dr. Insel: And let's hear from those on the phone, and maybe we can start with Dr. Klin?

Dr. Ami Klin: Good morning. I'm Ami Klin. I'm a clinician and investigator. I direct the Marcus Autism Center at Children's

Healthcare of Atlanta, and I'm the division chief for autism at Emory University School of Medicine in Atlanta.

Dr. Insel: And who else do we have on the phone?

Dr. Klin: I'm sorry. I was involved with Question 1.

Dr. Dennis Wall: This is Dennis Wall. I am a systems medicine expert working on early detection using genomics and behavioral data and also worked on Question 1. I'm from Harvard, and I'm actually in the process of transferring to Stanford.

Dr. Insel: Anybody else with us on the phone in the capacity as an expert who's worked on the Plan?

Dr. Kevin Pelphrey: This is Kevin Pelphrey, Kevin Pelphrey from Yale University. I'm a neuroscientist, and I direct the new Yale Center for Translational Developmental Neuroscience, and I'm the father of a little girl with autism.

Dr. Irva Hertz-Picciotto: This is Irva

Hertz-Picciotto. I'm an environmental epidemiologist at the University of California, Davis MIND Institute. I direct a program on environmental epidemiology of autism and neurodevelopment, including the CHARGE and MARBLES studies, and I worked on Question Number 3.

Dr. Nancy Cheak-Zamora: Hi. This is Nancy Cheak-Zamora. I am from the University of Missouri and the Thompson Center --

Dr. Insel: Could you speak up a little bit? It's hard for us to hear.

Dr. Cheak-Zamora: Yes. Is this better?

Dr. Insel: Much better.

Dr. Cheak-Zamora: This is Nancy Cheak-Zamora. I'm from the University of Missouri and Thompson Center for Autism and Neurodevelopmental Disorders. I'm a health services researcher and focus on quality and continuation of care for young adults with autism. And I did Questions 5 and 6, excuse me.

Dr. Insel: Anyone else on the phone?

So I believe David Amaral will be joining by phone, but not on yet since it's 5:30-something in his time zone. Lisa Croen and Paul Shattuck? So hopefully, we'll hear the beeps later as they join. Oh, and Silvana Borges as well. Okay.

Well, if we can advance the slides? We'll need to go forward one more, one more. Ah, thank you. Perfect.

Just take a moment, and there, I think, are only two slides. So for those of you at this end of the room, it won't be too much cranking of your neck. I just wanted to set the stage for what we need to talk about, and for those of you on the phone, I'll walk you through this so that you can get some idea of what the task is. And then, as I said, I'll turn this over to Susan to run most of the discussion today.

But for those of you who are not on the IACC, the drill was actually quite straightforward. We were tasked in the Combating Autism Act with creating a

Strategic Plan and doing an Annual Update of that Plan. The Act goes for 5 years. It will be finished in September of 2014. So we're in really the last year of this effort.

We created the Plan in the beginning, and that was released in 2009. And so what we have been doing is tracking the portfolio -- not just of the NIH or of CDC or Department of Education, but of all Federal agencies and now all private groups as well who fund autism research.

And I just want to underline that this is a Research Strategic Plan. There are a lot of other issues the IACC is tasked with dealing with, but this is just on the science.

So we have looked at the portfolio from 2008 until the present, and what the Committee decided to do this year for their Update was to do an accounting exercise. And specifically, we as a group said we're not going to add new elements to the Plan. We're not going to revise the Plan or rewrite the

Plan or create anything new. We want to take this year to see how have we done.

We set out this very bold agenda in 2009. We revised it in '10 and '11 by adding some new elements. I think the final number got up to something like 78 objectives. But we thought this was the year simply to do the accounting.

And the accounting was on two fronts. One was to say how much was invested in each of the various objectives, and then what did we get for that investment? What do we know now that we didn't know in 2009 or 2008, which was the baseline year in terms of portfolio?

The other thing that we wanted to do was to get some idea about whether there were new opportunities that had emerged since 2009 or even since the last Update last year that needed to be considered. And whether there would be an opportunity to in the next time this Plan is revised to highlight something that wasn't there before.

In the discussion that we had as a Committee, there was also some feeling within the membership that 78 objectives were just far too many, and it would be really difficult with so many things on the "to do" list to get -- maybe to get them all done or maybe to get any of them done if we were so unfocused. So there was some conversation about could we narrow this down? Could we define some priorities?

But I think at the end of the day, the group said maybe, maybe let's see what we've got first, and let's really do this accounting exercise, and then we can figure out if there's a way that we can focus better for the next version of the Plan or maybe make recommendations about what this might look like next time.

So this was the process that we went through. And we have done this on a very tight time schedule, made more complicated by the Government shutdown, as well as by Government changes in travel regulations and

regulations for conferences. I suppose if we were going to do a Strategic Plan today, it might be on some of the Government policies rather than on the autism objectives themselves because this has made it really complicated.

But Susan and her colleagues have still somehow managed to get us all together, in spite of having to change plans many times, and to figure out ways to help people to get to these meetings when it's been made very difficult.

There was an initial call with each of the groups that were set up around each of the seven questions, and that was really based on a chance to look at the portfolio analysis that was done by the Office of Autism Research Coordination, Susan's group. And I must say, this was a huge effort that they undertook to drill through all of the sources of public and private funding on every one of the objectives to say where are we, what have we actually spent, and who

spent what, and how does that look?

And they not only did it for now, but they did it over time. So we could see the trend lines in different areas, which is really kind of extraordinary. The first call was simply to go through that portfolio analysis and to say, given that each of the objectives that were laid out in 2009 had recommended budgetary requirements, where did we end up?

Did we spend that kind of money? Did we spend anything? Did we spend more than what was recommended? And how can we just do the simple financial accounting? How can we match dollars spent to what the recommendations are?

And I think all of us who do science know that these recommended budgetary requirements are absolute guesswork. We never know because the cost of doing science changes. Some things become much more expensive. Some things become really inexpensive.

And frankly, if we were really smart, it should cost us much less. Much of the money goes into what we call “opportunity costs” because we don't know what will work and what won't, and so we spend a lot of time learning what doesn't work often.

That's the way science goes. It's not like building a bridge. It's much more like exploring an unknown continent, and you just can't expect to always get on the fastest trail until you've really mapped out the territory.

So we're still in autism mapping out a lot of territory -- very difficult to know how much things are going to cost. But we did this as an exercise, and it's still useful, I think, to look at how the numbers match up.

Once that was completed, then we had the second call with experts who are brought in from the outside to basically say where are we in terms of the science on each of the objectives? And given what we have invested, what have we actually learned? Are there

objectives that could now be considered completed? Are there objectives where what we had originally intended to do probably ought to be shifted in some way because there's a new understanding of the problem? All of those kinds of issues.

And it's kind of amazing how, over 5 or 4 years, things really have changed in so many areas scientifically, where we have absolutely new opportunities that we didn't know about.

At the end of that, I think we had a pretty good idea of where we were and enough to be able to put together a brief summary, maybe a couple of pages on each of the -- of the -- seven questions that would capture what was spent and what did we learn. But we felt as a group that we really needed to get a deeper conversation that would bring together all the experts from all the questions to kind of look across this whole thing and to have some forum for really talking about where are we now and looking at

what's been done in this -- in these first two calls. And that's the task of today.

So today is -- the hope is to have the IACC and all of the invited experts hear about the results from all the phone calls and then to try to refine what the final document would look like, which will be part of this Update on the Plan.

Again, I can't stress enough that we're not going to be adding new objectives. I don't think we're even going to be taking out objectives. But what we really want to do is what the IACC asked for a few months ago, was to say where are we now based on what we've done, and how has the Plan worked?

Just again, another sort of 30,000-foot comment, this is a really interesting exercise for someone who works at NIH. We don't actually do this very often. We don't have a refined Strategic Plan like this and then look 5 years later to see what's come out of it.

And I think, if nothing else, just using

this process as an assessment of whether having a Plan like this is helpful or not will be useful for the funders. And that, in itself, getting some reflection about that can be very interesting.

The task for today then is we'll go around and take each of the questions in turn, have a conversation about -- from the co-chairs who have led each of these questions and from the experts about where we're at. We'd like to get input from the whole Committee and from all of the experts. So even if you were assigned to Question 5 and you hear something in Question 1 that you think needs to be refined, let us know. Don't feel like you have to wait until your question comes up.

This is really meant to be very much an open forum. We'll have some time in the middle of the day as well to hear from public comments, those who are not at the table yet, and have them tell us about their thoughts on this whole process.

We want to end up by the end of this day with a chance to take the summaries we've got and tweak them a bit, and then we'll be getting those back to the IACC in pretty short order so that we'll have a finished document by the end of December that can meet the statutory requirement of having an update done each year. So this will be the Update for this year.

So that's a really quick run through. Susan, anything else to add?

Dr. Susan Daniels: Do you want to have a couple more people introduce themselves?

Dr. Insel: Yeah, we will in just a moment. Susan was just pointing out other people have joined us. So if you've joined since we started?

Dr. Walter Koroshetz: Hi. I'm Walter Koroshetz, deputy at NINDS, NIH.

Dr. Insel: Anybody else who's joined?

Dr. Silvana Borges: Silvana Borges from FDA.

Dr. Insel: On the phone?

Dr. David Mandell: Hi. This is David Mandell from the University of Pennsylvania.

Dr. Insel: Welcome. David is a member of the IACC.

Dr. Maureen Durkin: Hello. It's Maureen Durkin from University of Wisconsin.

Dr. Insel: Great. Welcome. Maureen, which question did you work on?

Dr. Durkin: Sorry. On Number 7, the surveillance and infrastructure.

Dr. Insel: Thank you. Anyone else who has joined?

Okay. Susan, any other overview comments?

Dr. Susan Daniels: No, I think you've covered the overview. Hopefully, since we just had the second round of calls within the last week, everyone's memory is quite fresh of what we just discussed. And we really look forward to having everyone be able to open up what's been discussed on these individual phone calls and to get some crosstalk going during this meeting.

So with that --

Dr. Insel: So before we start, let's just see if there are any questions about the overall process or where we're at here, or what the goal of the day is. Any questions at all? Should be an interesting conversation just to get a sense of where people think we're at.

Walter, go ahead.

Dr. Koroshetz: So I was just thinking, and maybe I missed this. And I apologize for being late. But would it be reasonable to kind of outline what needs to happen in the next month and a half, I guess, is that right, based on our conversation today? So that might help frame --

Dr. Susan Daniels: Sure. So the slide here talks about the things that have happened and the workshop. After the workshop, we'll be asking for volunteers from each of the planning groups -- IACC members from the planning groups -- to do short write-ups. And so this work was supposed to

have started before the shutdown, but then the shutdown, unfortunately, kind of got that a little bit off track.

But we've been carefully documenting what has happened on these calls, and we have information we can give to each group. I know that we already have some volunteers, and we might need some additional volunteers. But we're expecting short write-ups. So hopefully, it won't be too difficult a task and just summarizing the outcomes from these calls and the workshop.

And after that first set of documents comes through, we'll have the planning groups look at them, and after that, once they've been refined there, they will go to the subcommittee chairs to look at them across the entire Plan to help unify it. And then we will have a meeting by phone of the entire IACC to vote on the final document.

But at this meeting, all members of the IACC have been invited and have an opportunity to weigh in on the work that's

been done so far. So we hope that most of the major input will be coming in during this part of the process and not at the very late stages after we've done most of the writing.

Dr. Insel: In terms of timing, when do you -- what's the due date?

Dr. Susan Daniels: So we will be aiming to have a final document, all the final text before the December holidays. Because then we are supposed to have the text done within the calendar year, and then the pretty document will be released in the early part of 2014. But all drafts, of course, will be publicly accessible on the Web in the meantime.

And all of the drafts from everything that we've discussed so far in this process, they're all available on the Web. All the materials for today's meeting are also on the Web. If you go to this meeting's Materials link, anyone from the public has the same documents that have been provided to the Committee and to the members of this group.

Lyn?

Ms. Redwood: I was wondering if we have notes from the meetings, the second call. Because I've noticed some of the experts that were on those calls are not actually here today.

Dr. Susan Daniels: So the minutes are not complete. As you know, those calls just happened, and so we haven't been able to complete the minutes. But I did provide you with documentation of what basically the major messages were from those calls, and you have them in your packets. And they were emailed to you last night. So you have them, and they're up on the Web.

And so those are really -- they boil things down. They don't have all of the details that the minutes would have but hopefully captured most of the main points. And if we didn't capture something, hopefully, here in this room today, you will be able to point that out and let us know so we can make sure we take note of that.

Dr. Insel: And certainly, there should

be somebody from each call, from each of the second calls, to be clear, in the room. So -- or on the phone so that we can get a pretty good reflection of what was in the conversation and make sure nothing is left out.

Any other questions or comments?

Dr. Hertz-Picciotto: This is Irva Hertz-Picciotto. I have a question about you indicated that this is the workshop dealing with the science, and not being on the IACC, I'm actually not sure what the entire purview of the IACC is. I'm wondering whether there is a separate process or similar kind of exercise going on in relation to issues like translation of science?

Dr. Insel: I'm not exactly sure, Irva, what you're thinking of. Maybe could -- if you could just be a little more specific? What kind of question -- what kind of project are you thinking about?

Dr. Hertz-Picciotto: Well, I'm thinking in terms of science that has, you know,

implications for sort of next steps in relation to whether it's screening, diagnosis, prevention, you know? As you know, I'm on the environmental side of things. So I'm thinking in terms of translation of some of the work that's been conducted on, for example, nutritional factors and --

Dr. Insel: Right. So --

Dr. Hertz-Picciotto: -- is that something that might be getting discussed elsewhere or maybe isn't, but is something to think about?

Dr. Insel: If it's science, it should be -- if it's science relevant to autism, it should be within this Plan. The IACC does lots of stuff that's not within this Plan. We have groups that work on policy issues, groups that are very concerned about services that are not at this point research topics as much as topics related to financing, housing, educational supports -- a whole range of issues.

Those aren't part of the Plan. That's a

separate part of what we do. Our mandate is to advise the Secretary on virtually everything related to autism as it plays out in the Federal Government, and that's not simply HHS, but across the Government.

So I'm not sure if that answers your question. But if -- if you're asking about translational research, it should very much be covered in one of the seven questions.

Dr. Hertz-Picciotto: Yeah, I think I was thinking more in terms of translational -- translation to policy. So maybe that's really where it does go.

Dr. Susan Daniels: The IACC is an advisory group, and so the information that's provided by the IACC provides advice for Federal agencies in order to be able to carry out their missions in relationship to autism.

Dr. Hertz-Picciotto: All right. Thank you. Thank you very much.

Dr. Insel: I think we say this at every meeting. Often it is misunderstood that this group is advisory, and it has no budget. So

what we do is to provide a picture for others to know what's being done in the hope that we can coordinate the work or we can have some impact on policies.

But we don't have any opportunity to fund science ourselves, unfortunately. So it's most, at best, having a bully pulpit is what we can do. Okay. Anything else before we start?

Let's -- Susan, I'm going to turn this over to you, and we'll start with Question 1.

Dr. Susan Daniels: Thank you.

So just to give you a brief orientation to what the information is in the materials, we provided you with the cumulative funding tables that were used on the first call, and all seven chapters' worth are in your hands in one packet now so that you can see everything. And so if you need that as a reference today, you have that in front of you.

And for Question 1, we've provided a summary table that goes through each of the

objectives and provides a very brief summary of what was discussed on the two calls, synthesizing that information. And on the slide in front of you, we have listed the aspirational goal for Question 1, which is, "Children at risk for ASD will be identified through reliable methods before ASD behavioral characteristics fully manifest."

And this was the aspirational goal that the IACC wanted to reach for as it developed this Plan and determined what types of objectives would fill in some gap areas in research that would be needed to reach this aspirational goal.

And below the aspirational goal, I've provided a few brief bullets of key themes that were heard on these calls. And if anyone has any corrections to those, you can let us know. But to get us started on Question 1, to find out, you know, what else do we need to do, what do we think is the health of Question 1 of this area, diagnosis and screening?

We won't have time to go through each objective individually the way we did on the calls because we have a shorter time period. But you have in front of you the summary.

So some of the main themes that we heard on the phone call were that we need cost-effective, performance-based screening and diagnostic tools, that we need tools that are effective in diverse cultural settings. We need to link genetic testing with availability of appropriate interventions or other benefits. And we need biomarkers of ASD risk.

And so how do you feel about those particular takeaways that we've identified? What else is needed in this area, and what might not have been covered through the objectives that exist in the current Strategic Plan and through the work that's been done, the work that's been funded, and the results that have been coming out of research in the past 5 years? So this discussion is open to anyone.

Dr. Insel: Maybe we could start with somebody who was on Question 1? From the IACC, is there -- who was? John? Okay, go ahead.

Mr. Robison: My -- my concern, I guess I volunteered to be the chairman to write Question 1 with Susan once again this year. When we went through our objectives for Question 1 -- and you'll see this looking at the sheet -- you can see that half of our objectives are marked in green that we, to a significant degree, achieved them, and most of the rest are marked in yellow, showing that we achieved substantial progress toward them.

Only one, which was conducting studies to understand the impact of early diagnosis on choice of intervention and outcomes, only one has not been attained. And that's because we have not been presented a project that would -- that would address that, that question.

So that seems like a pretty good

outcome. But I have a real concern, and I think this concern applies to all the questions. And I think that we should discuss here whether we would address this concern in our write-up about Question 1 or whether we would address it in a preface to all the questions.

And that is this: We -- we asked these various questions, and we say to ourselves that we answered them. We look at developing a diagnostic instrument, for example, and we have -- we have funded research that's delivered us good results. But what we haven't done is translate that work and deliver it so that it is accessible to the public.

I think one thing we need to do -- it's very important here for our connection between the IACC, the Government scientists, and the autism community -- we need to acknowledge that even though we have funded the research and the research has yielded valuable results and valuable insights, we

have not translated that into anything of substantive value for the community.

And I think we need to address what our plan is to facilitate making that happen because that's, you know, obviously the true objective that the American public has for us in doing this work. I know that that's a -- it's a difficult question because the scientists involved in this, they say, well, we funded the study, and I got the results, and I did my job. And I absolutely agree with that. I have no -- no issue with it.

But I think that we didn't really foresee the complexity in translation, and most importantly, we didn't present that complexity to the public so that when we tell people that we're doing this work and they think, okay, you're going to get a result in 2 years, and then I'll have help for my kid a year later. We didn't really make clear that that wasn't realistic.

And -- and I think that we have a duty to do that, and I think if we don't do that

as a key part of our Strategic Plan, we are going to be subjecting ourselves to tremendous criticism. I think that's the foundation of the popular public argument that we don't do anything, when those of you around the table, you know that we do do a lot. We fund a lot of valuable research, but we've got to get it to that next step.

With that, I guess I would ask for thoughts of the Committee on where we're going to -- where we're going to speak to this question, in a preface to the whole thing or Question 1.

Dr. Insel: John, thanks. I think there are going to be a few of these cross-cutting issues that will come up because this is not only relevant to Question 1, it's going to be all the way through. So --

Mr. Robison: Oh, yeah. It's all of them.

Dr. Insel: So let's bookmark that one.

Mr. Robison: Okay.

Dr. Insel: And we'll come back to it as we think about what the final document will

look like and whether there can be a section either at the beginning or the end.

The other cross-cutting thing I think we'll hear about today are those things that were never in the Plan that could now become really a great new opportunity. And I think we'll capture a few of those as we go through the day.

So we'll want to just collect some of those, and then we'll think about it when OARC puts together the report, with your help, that we'll find a way to flag each of those issues, either at the very beginning or the end.

Walter?

Dr. Koroshetz: Yes. So, John, I appreciate your comments, and I'd just ask maybe yourself or other members of the group to think about, you know, it seems as though you were thinking that some of the results could go right to policy and make things accessible. But there's usually research that's needed along that pathway.

So for instance -- develop a drug or a diagnostic -- the first step is usually to identify, you know, some value proposition that this new diagnostic brings. The second step is usually to go into a multicenter study to look and see how that technique -- how robust are its findings and whether it really truly does what the investigators first thought it would do when it goes into a more general population.

And then the third thing is -- which is the tough one, is to try and prove clinical value or clinical outcome to the diagnostic. So I guess my question to you is, in this, is there research needed, do you think, to move some of these promising discoveries to the point where it's going to be FDA approved, let's say?

Mr. Robison: Yes. First of all, I agree with what you're saying, and I'm aware of that. To some extent, I see one of my big roles on IACC as translating the science that we talk about for a non-science community,

and I don't think the broad public understands the significance or truth of what you've just said. And I think that we need to convey that.

When you ask if I think that there are studies, I think that, yes, I think that we should talk about a process by which we go from the basic studies that we've done here to validations. And then to go from validations to develop a plan to train people to disseminate the results of the studies and then to begin to implement that.

And my concern is that that's a pretty slow process. It's going to take a number of years, and I don't see a real way that we're going to short-circuit it and make it happen in 1 or 2 years. I think, therefore, that we have a duty to the public to lay out what could be a realistic expectation of when benefit could be in the hands of the public from these things.

I absolutely understand what you're saying, and I guess I think it's a task of

informing a public who has perhaps come to doubt our effectiveness or capability because we haven't helped them to understand the true scope of what we're trying to do.

Dr. Insel: So since we have so little time, I want to just make sure we get to the work of these specific objectives in this question. What we'll do, what I'm hearing from you, John, is that there is some sort of managing expectations that we need to address. And I think we can do that quickly in the final report.

So we've marked that down, and we'll -- as I said -- we'll come back to that as part of one of the cross-cutting issues. It's going to be true through every one of these questions. There is an opportunity, I think, to educate people about how science is done, how it gets translated.

And remembering that a lot of what we do scientifically is to prove what doesn't work and what people shouldn't do. It's not just always the breakthrough about the next best

thing that people need to translate. So we have both roles here.

I think I saw a couple of hands up. Karen, did you have a comment about this objective?

Dr. Pierce: Yeah. I think it's exciting to see that a lot of the objectives have been met. But one of the objectives is to, you know, identify biomarkers for risk for ASD, and what I'm seeing in all the kind of -- the great research that's come out on early biomarkers, a lot of them are focused on using the Baby Siblings design, and which represents autism as it occurs in multiplex families.

And I'm not sure -- you know, the jury is out whether or not the etiology of autism is the same in multiplex families versus simplex families. So I just would like to see a little bit more of an emphasis on using general population-based approaches to detect autism early, like we do in our center, starting at 12 months, to try to discover

some biomarkers.

I know like Deborah Fein's group are using screens to detect autism early, but really more has the end goal to determine the validation of that particular screen, not necessarily to discover biomarkers of autism using a general population screen. So I just would like to say that there are great biomarker discoveries that have been made, but they're very Baby Siblings design centric. So that's maybe part of Question 1 that hasn't been fully met.

Dr. Insel: Yeah. So let me just stay on that comment because I think there are two issues on the table. One is have we met the financial commitment that people first recommended? And as I hoped I said at the very beginning, there was a lot of hand waving that went into those numbers. We had no precision, and this is not like engineering where you can say if you spend $10 million, you're going to get the bridge that you wanted to build.

So we don't know if it's going to cost much more or sometimes much less, if we're really smart. So I think one part of the question is have we done the financial commitment that we originally set in 2009? The more significant one for today is what have we gotten for that, and where are we in terms of this aspirational goal?

So when you say that we've met the objectives of this question, I mean, would you -- if you look at that, "Children at risk for ASD will be identified through reliable methods before ASD behavioral characteristics fully manifest." Are we there?

Dr. Boyle: Can I -- no. I was going to say, can I just say a few things for Question 1, since there are a few of us. John, unfortunately, wasn't able to participate on our last call, which was a couple of days ago. And I think we had a very rich discussion.

Ami, who is on the phone, as well as Geri, were there, and myself, and I think

there was one other person on the call. And I did feel that we've -- I mean, this is a wonderful summary of what we had talked about, that there clearly has been progress made. But there was a long way to go, both in terms of the, you know, efficient, effective diagnostic tool, screening within the context of diverse settings and general population settings as well, sort of really taking that more or not from an efficacy to more of an effectiveness model.

The genetic testing and its benefits, that's clearly a very open question and one that, you know, we were hoping that the American Academy of Pediatrics looks at in more detail. And then really the biomarkers of risk. You know, a lot going on, very rich studies. But in terms of their application or their ability to be able to screen populations, we felt there was -- you know, we were a long way from the goalpost there.

So I thought it was a great, rich discussion, and I don't know, Ami, if you

wanted to add additional context to that? But we -- it was a very different tone than our initial meeting in terms of actual dollars that were being focused on this area, but to actually what was realized in that context.

Dr. Klin: Well, we all felt that there are some promising lines and even some good discoveries that we need to address the issue of translation very seriously. And the issue of translation involves a series of steps that there's no way that we can shortcut this process from small studies to large replication studies, from models that are lab based to systems that can be deployed in community settings so that we address autism as the public health challenge that it is.

And the issue of reducing age of diagnosis cannot be decoupled from improving access to care, and so the commitment to developing those systems with equal energy bringing the science to the community, and quite a bit of work has been done on that, too. So I think that it was an optimistic,

but certainly a very realistic sense that from lab to a community tool, it takes work.

And thirdly, just to emphasize, is that all of those research studies and designs, they are really fraught with value questions, and the bioethics of this is something that we all need to embrace and advance. Because without addressing those issues, the whole research and progress could be undermined, and things such as genetics and genomics testing are something that have been given a great deal of attention to, but some of the other things are equally important, including some of the issues that I heard previously in the call which have to do with the fact that we need to develop systems that don't work simply for a very small group of people, but they address the vast majority of individuals impacted by this condition.

Dr. Insel: Can -- I'm going to do this throughout the whole day, I'm afraid. But I'm going to ask you to help us by getting as specific as possible on this.

So in this case, if the question from the aspirational goal is identifying children who are at risk before they manifest symptoms, and if that's -- sorry for the football metaphor -- but if that's the touchdown, are we on the 30-yard line or the 50-yard line or -- so to be really specific, if there are 100,000 children who will be diagnosed by age 4 or 5, and if we are starting at age 1 or before, what percent of those kids -- with the current science that we have -- what percent of those kids are we able to detect before they have manifest symptoms?

Can somebody give us just a sense of where we are, and where is the -- where is the -- current mark for that? Karen, do you --

Dr. Pierce: Are you saying what's possible or --

Dr. Insel: What's -- in a laboratory setting. Where is the science telling us? What are we able to do scientifically?

Dr. Pierce: I think it is possible to detect. No one has done a real study to show exactly what the sensitivity level is. If you, let's say, started screening with a broadband screening at 12 months, and you did it at 18 months, then you did it at 24 months, I think we could detect 95 percent of ASD babies.

I think it's possible because, you know, there's a slow and gradual onset of symptoms in ASD, and I think with repeat screening, you would be able to detect a large number of those kids. It's just it's never been quite done on that earnest level before.

Dr. Insel: Before -- so just to go back to that goal -- before behavioral characteristics fully manifest. So you're saying 95 percent of kids could be detected before?

Dr. Pierce: No one's done the study. I can't say for sure. But I know that, yeah, you know, you can see lots of early emerging symptoms in lots of kids. The issue is that

it's hard to get pediatricians to follow through with repeat screening and et cetera. There's all these barriers that you'd have to overcome.

But I think from a scientific perspective, based on what we understand in symptom onset patterns in autism that really between 12 and 24 months or 12 and 30 months, they're coming on, they're coming on, and they're coming on. And if somebody is checking in regularly every 6 months, you would catch it.

It's just the question is that people are not checking in every 6 months, and they're not doing the appropriate -- you know -- those other steps along the way are not happening. But theoretically, if you could get people to do it, I think we have the tools available that we could do it, and it can only improve from there because there are other things you can add on, like eye tracking and blood tests and things like that that could just, you know, make incredibly

powerful. But theoretically, I think it can be done.

Dr. Insel: So I think that the report that we do at the end of the day, or maybe I should say at the end of December, it would be really great if there is some very specific comment we can make, sort of like where are we in this? Knowing that this is the goal, are we 30 percent, 50 percent?

And you're saying 95 percent potentially. That's --

Dr. Pierce: Theoretically. But the reality is it's more like 2 percent. I mean, you know, people don't really do this, but theoretically, we could.

Dr. Insel: Well, so I think there are two different issues, and one is what this is saying is that children at risk will be identified. What would be helpful for us to establish first is where is the science? Do we have now the tools to do this with accuracy? What is the false positive, false negative rate, specificity kind of questions?

It would be helpful to sort of lay that out. Sensitivity and specificity 2013. I think we have a pretty good idea of where we were in 2009 on this, which was very, very low. So where have we come in the last 5 years?

Anshu?

Dr. Batra: Thanks, Tom.

I think, to answer -- to try and answer your question -- I think the first part, in terms of the funding, I think, clearly, the funding has been there. And again, I speak from a perspective as a general pediatrician and a developmental pediatrician, having done this over 20 years. And actually, we are checking for signs, actually.

I think -- I don't think there's a pediatrician, you know, in this room or outside this room that doesn't look for autism anymore at 12 months. You know, is the child making eye contact? Is the child pointing? I think that that's -- that's -- probably one of the first things we ask

about, along with all the other directives we have.

I think the issue here is what specifically we are looking and asking about. And if we're specifically asking about behavioral traits in autism, such as language and behavioral manifestations, I think we are missing the boat here, to be honest.

I think that the features, some of the symptoms are actually evident earlier than the behavioral manifestations and the manifestations that I think that we're sort of used to looking for. They are -- they are -- latecomers in the autism sort of spectrum development.

I think we have to start looking at the early, early things in a child's development, 0 to 12, which, again as a pediatrician, the things we look at early on are the motor development, the tone, the symmetry, the motor planning then the joint attention and then verbal and behavioral traits.

And so I think that, yes, Karen,

absolutely. I do think that if we're looking for the symptoms that, you know, for autism as of now, yeah, I think -- I think that we have the ability to identify the at-risk population. But I think that we are not looking at the right markers.

And I think that if we look at the earlier motor development, the earlier stages of development, 0 to 12 months, we can then identify those individuals that may be at risk not only for autism, but other developmental delays, because all children who have delays in development 0 to 12 months don't all have -- don't all go on to develop -- autism.

And so I think that we have developmental tools that I've been trained for 20 years on that we could use to identify the at-risk population, and then see what percentage of those individuals go on to then develop the behavioral patterns of autism as opposed to other developmental disorders that we see commonly in childhood.

Dr. Klin: Tom, if you don't mind, this is Ami. There are some community realities. I just wonder if Amy Wetherby would like to just to comment on that and try to bridge state of science, state in the community for us, if she is on the call?

Dr. Insel: So Amy is here. Joe Buxbaum also has a comment, and Geri as well. But I just want to frame the question in two ways here. One is I think there is -- according to the aspirational goal -- there is the challenge of what we are currently doing in practice, and we've heard about that already. It would be helpful for the Committee to know where is the science?

So what's the best case based on current research, whether it's work that you've done, Ami, work done by Phil Teitelbaum in 1998 on motor patterns as predictors, what we have from genomics, all of those issues, how far along are we toward having something that could be used in the community?

So, Amy?

Dr. Wetherby: Thank you. I did have my hand up, Ami, thank you very much.

So I want to make a couple -- I'm going to try to be as efficient as possible. A couple points and tie a number of comments made together with your last comment.

One is I think we need to begin to separate out how much we're investing in younger sibs versus community samples. So I think that we are learning a lot from the younger sibs. It's a very important part of our advancing science, but we need to -- and maybe this is a recommendation -- think about how much are we investing in looking at community samples and making some equal investments?

I think, as Karen raised, they may be very different, may provide us very different scientific information if we get more simplex families.

Secondly, I think that by investing more in community samples, we're going to understand more about the health disparities.

So we can talk about what we know in the lab, but when you begin, my research, and Karen has done this as well, is focused community samples. And so when you're screening in community samples, you lose a lot of families. They don't come in, and understanding who doesn't come in is very critical to understanding the science that we now have.

Thirdly, I think there's this very complex challenge when you try to do the science, and it's the same problem with the service in communities because the doctors may be using tools that are 20 years old or newer tools. Most of our tools are based on cutoffs that go along with the eligibility criteria for early intervention, which is two standard deviations below the mean.

And that means you're never going to get more than this 2 percent of the population. But yet when we get to school age, 11 percent are served in special education. So we have this huge gap in the early-intervention

system, which is partly reflected by the screening tools we have.

So we have tools, and they're good at catching the bottom second percentile. You're going to miss all of your higher functioning individuals. You're going to miss your moderate-functioning individuals. You're going to catch your individuals with more severe disabilities with obvious medical or physical risk in the first year or two of life.

And so I can give you -- one quick example is the ages and stages, which is probably the most widely used broadband screening tool and the best sensitivity and specificity, which are in the 80s, are -- is based on the second percentile. Now we've developed a screening tool that Karen's lab has used, the Infant-Toddler Checklist, and we have our cutoff set at the 10th percentile.

The problem is then those children don't qualify for early intervention. So it's this

-- you get into ethics. You're screening, but then they can't get services. So there are policy changes that are needed. So this is very complex.

With our screening tools going up to the 10th percentile, we've actually been able to catch a lot of children with autism that way. So it's exciting. So I do think the science is moving. We have gotten a lot of funding to develop some new screening tools that have a lot of promise. So I don't want to get into details on them, but parent report, observational measures that we have a lot of data and papers either under review or in process that are very exciting.

Dr. Insel: But can we get to -- I mean, are there numbers for sensitivity and specificity? At least that's what you'd ask for any other illness. What's the problem --?

Dr. Wetherby: Well, I think in general we have sensitivity/specificity on our screening measures on more and more different samples, and everybody is aiming for above

0.8 -- you know, 80 percent. And so sensitivity/specificity are in the -- ours are down to 12 months up to mid to high 80s.

Dr. Insel: So you're saying that at 12 months, it's over 80 percent sensitivity and specificity?

Dr. Wetherby: Yeah, yeah. And what we're finding, going back to your motor, is that early gestures are the most important thing to ask parents about. I mean, part of it is, is your screening based on observation or parent report, and what do parents notice?

So what we're finding with our tools that early gestures, you know, children should give at 9 months, they should show at 10 months. They should wave at 11 months. They should point at 12 months. Parents notice these gestures. They're pretty good at reporting them.

So we have a lot of questions about gestures, along with many other behaviors. And so that is helping to get children in early, and some of them are going to have

communication problems as well. But then when you start to ask more about repetitive restrictive behaviors, then you can sift out children that have autism.

Dr. Insel: So I want to make sure Joe has a chance to add to this, and then we'll go wider across the room.

Dr. Joseph Buxbaum: So for the genomic perspective, I do think with existing data, which has not been fully analyzed yet, or emerging data, we can identify 30 percent of kids that have a genetic finding that will increase for risk. So if you want a specific number, 30 percent.

But I do think that we're going to -- I don't -- I think that the T2 translational point is being missed here. I think you're right. We have tools that are 20 years old. We have newer tools that are emerging that capture kind of late -- kind of pre-manifestations and earlier manifestations like motor. But even the things that just catch later manifestations that have been

around for 20 years, those are not being fully deployed. I just don't think they are.

And I think the T2 mission is not just about getting the word out to the population, but kind of the NIH and other organizations asking good questions about why things that exist are not being deployed. And when they are being deployed, why don't they translate to an intervention or referral to an expert site? And the questions, one of them, of course, is about funding, you know, for that person and so on.

But that question, I think, is we're making better and better tools, but the tools that we have that sort of work maybe late in the process aren't fully being deployed. And I agree that with the motor -- we're getting better and better at going earlier and earlier, and motor is clearly one of them from the infant sibs, as well as from population based. But if we can't even get the later ones deployed, I worry about developing better and better earlier ones

that are also not deployed.

Dr. Insel: Anshu and then Paul and then Scott.

Dr. Batra: Well, I wanted to comment on Amy's comment about -- I agree. I think the early gestures, early communicative gestures, you know, at 9 months, 12 months, are ones that need to be in place. But I think even earlier, the visual component, the visual attention and the tracking along with the motor is something that is -- is -- evident early on that I think we're just -- we're not looking at that, at those signs and symptoms and then relating them to the, you know, the at-risk population for autism versus other childhood developmental disorders.

And lastly, you know, I have to comment on what John had started out by saying that, you know, I think we on this Committee have a -- we serve a role. We have a voice, and we owe it to the community, to the parents to let them know that, yes, billions of dollars have been spent on this, but we've made a lot

of progress in terms of science, but little old me sitting in southern California, what do I have that I can take to my patient and offer them?

And that's what I feel that I'm at a loss. That we can't -- we owe it to the population to let them know that that -- that has to be one of our objectives, to take what we've learned and apply it.

Dr. Insel: Anshu, question. Just again, a point of clarification. The Michael J. Fox Foundation for Parkinson's has just released this very interesting cell phone app that detects Parkinson's by changes in the voice and is going to be deployed worldwide. Very inexpensive.

It's what's called a passive diagnostic. So you don't have to do anything. You simply have to call them, and they capture the data. Is there something like this for looking at visual, motor, attentional issues? Do we have anything that would be comparable?

Karen, I know you've developed video

tasks like that. Is there something, though, that's out there, since this is we're talking about community samples, general population, looking at when should I be concerned? Do we have something for the public that's available like that?

Dr. Pierce: Not yet. I mean, we're doing some validation statistics in pediatric settings, and if that works out, then maybe one day. But you know, the risk, I think, for something like this with a developmental disorder is you have a bunch of moms with cell phones, you know, with a lot of anxiety and false positives. It seems like there would be a lot of research that would need to be done to get to that point.

But I think it's feasible, but I don't think we're there yet or close to being there yet.

Dr. Insel. Okay. I think, Scott, you had your hand up?

Dr. Robertson: So I just wanted to make sure to get this comment because I knew that

we would eventually be in a short amount of time be running out of time, I presume, at some point on this question. It's okay if I have a comment on one of the objectives?

So one thing I did notice on the funding and the prioritization is that there were the workshops that were previously held on the ethical, legal, and societal social kind of aspects of doing this research, which happened in 2011, and then nothing has kind of happened since then. And it seems like a large -- and that should be a significant part of the impact and translation is considering those aspects on an ongoing basis, and it does have a comment to that effect.

Yet it's interesting to note that the funding in terms of the large funding has gone into all these other objectives, and it really stands out to me when you look at the ethical, legal, societal area that we did. It's like the workshops were done, and that's all we had to focus on that.

So that does give me large concern that that's not an ongoing conversation to be having them more regularly than just having them at one point, having a few of them in 2011 and then stopping. Because -- as this -- as we advance for this objective on the science for diagnostic assessment, et cetera, and this is going to be applicable, I would presume, for the other objectives as well, more thoughts come up and more considerations come up related to the ethical, legal, and societal kind of implications of doing this work in science.

So I would hope that maybe in the upcoming future, in the next couple of years, maybe there would be space maybe to hold some more ongoing workshops in this area so that we can keep on par with the science that happens in this area and for the other objectives, and we can continually be looking at those ethical, legal, societal issues.

Dr. Insel: Yeah, thanks. I think that's an important cross-cutting comment. You know,

the reason I keep pushing you on sensitivity and specificity and false positives is I keep thinking about one of the most widely used biomarkers in medicine is PSA for prostate cancer.

The people who developed that have apologized, and they have requested that no one use it anymore because it's actually created more harm than good because it has -- even though the rate of false positives is not that high, the implications of getting a prostate cancer diagnosis just from PSA or getting even further diagnostic workup has more complications than having the diagnosis often.

So we have to be mindful of all of those issues in going into this, and I think it's an important cross-cutting issue as we think about it.

Let's go around this way and, then knowing that time is short, make sure we capture comments. Paul?

Dr. Wang: Paul Wang, Autism Speaks. Back

on the translation issue that John Robison initiated, I think that Joe Buxbaum next to me here said the most important word, and that's "deployment" of the tools that we have, of the methods that we have.

As I look at Question 1 here -- I apologize -- I'm new to the IACC table this week, perhaps it's ground that's been covered. What I do not see is an adequate emphasis and support for research on health care services, on service delivery models. That's what we need to understand better.

There's a little bit of attention with the sub-question on disparities, but I think this is clearly what we need to do. The aspirational goal of identifying children at risk is actually two steps ahead of where we need to be. We need to identify children who have ASD earlier than we do, and we need to understand why our current health care delivery system is failing to do that as early as it can clearly be done and address that.

Dr. Insel: So, Cathy?

Dr. Rice: This has been a really important discussion about the need for community samples, and I think one of the things that's not reflected in our objective is that we are on the crux of an important opportunity to bridge science and policy and practice with recommendations that exist for screening, coverage of preventive services, and thinking about the future of how we can embed some of these objectives into the practice of what should be happening with developmental monitoring, general developmental screening, and autism screening.

And how does that help us understand these issues of sensitivity and specificity? A false positive is very concerning if it's a child that truly doesn't have any developmental delays or needs. But if we are only focused on autism, we may be missing and losing out on the opportunity to look at the range of functioning that kids have, the

support that they need.

So for instance, with the M-CHAT, although the very high rate of false positives, that's only the case if you look at autism as the outcome. But if you look at broader developmental delays -- communication challenges, other areas where kids still need early intervention -- it still can be an informative tool.

So we have to look -- you know, I'm very guilty of being autism myopic -- and that's where I think -- you know, that's what this Committee is about. But I think thinking about some of our research embedded into the broader picture of developmental delays, developmental functioning, and how we specifically support the skills that kids may need to be linked to intervention early is something we should think about for the next iteration.

Dr. Insel: Great. Jeremy?

Dr. Veenstra-Vanderweele: So I mainly wanted to make sure Zach Warren got a chance

to say something. But I want to make a --

[Laughter]

Dr. Veenstra-Vanderweele: He's hidden there in a corner. But I wanted to make a couple points, one is — It's -- yeah, it's difficult with this aspirational goal to separate screening, right, kids who really already should be identified as having autism, from what I see as the true aspiration here, which is to identify those kids before they have autism, when they may have some flags, when we may be able to do some—.

And I think we've made significant research progress in identifying kids who have enough signs of autism to think this child has autism, and I think that's really encouraging. I think we've done less well pushing that to T2 and moving that into the community.

I think we've made less progress with where I really see the aspiration, which is trying to understand the kids who are at

risk, don't yet meet criteria, and really don't have a whole lot pointing to the criteria if you're doing a behaviorally based screener. And that's where I don't think we have that much.

And we have tantalizing clues. Ami recently published one of these. Joe alluded to the genetics. But those aren't things that I think are particularly close to implementation, unfortunately.

So I would say we're certainly not, from where I read it, at 95 percent. You know, I'd say we're closer to those things that are robust out there in the community that are closer to 20 percent.

Dr. Insel: That's a pretty big range. Anshu?

Dr. Batra: Yeah -- oh, I'm sorry.

Dr. Insel: I'm sorry. Lyn was next.

Ms. Redwood: A real quick comment, Tom, about biomarkers and some of the information that, Anshu, you were talking about. There have been a lot of studies -- actually, 437

publications investigating the relationship between immune dysfunction and inflammation in ASD -- and 416 of those implicated a relationship.

But one of the things we don't know, Tom, is because this information has been collected after a child has been diagnosed, whether or not those markers of either inflammation or immune dysfunction might be present at birth. So I would really like to see us try to go back and come up with some more physiological biomarkers that we could be investigating at the same time that we look at PKU and thyroid. So I think that should be one of our goals as well.

That's very granular. Another comment that's a little bit more global is what do we do with these gap areas? So far the Plan has been investigator driven. There was one objective here that I think is very important in terms of what are the results of identifying these children early in terms of what their outcomes are and the therapies

that they use. And nothing was funded, or one study was funded.

So I think at our next discussion, we need to look at specifically how to fill these gap areas. Thank you.

Dr. Insel: Anshu?

Dr. Batra: Um, oh, boy. So I would have to agree -- I don't know your name. I'm sorry.

Dr. Veenstra-Vanderweele: Jeremy.

Dr. Batra: Jeremy, I would have to agree; 20 percent was the number I was thinking about right now in terms of being able to identify these kids early on. And I think that speaks to the issue of -- of really -- being able to identify really the heterogeneity of this population.

And yes, I absolutely agree with Amy. That 2 percent, yeah, you're going to pick them up early, all right? But what about the 98 percent that may be the higher functioning or the mild to moderates, and they're the ones who may be developing those symptoms

later on.

So we have to have some infrastructure in place to identify those populations, and I think, again, it starts with the -- as Lyn was talking about, I have a whole population of kids that I know have the risk factors for autoimmune disorder because of the maternal history and things that the parents have -- or I gleaned from obtaining a detailed history.

And I'll check, you know, blood work early on to look for physiologic and metabolic issues that might be contributing to the behavioral patterns I'm seeing in that child. And -- and to speak to your question, Tom, about, you know, an app similar to Parkinson's, no, we don't have anything like that right now because I think we're just -- we're not -- we're looking at the wrong targets, to be honest.

But in my community, I refer to -- to certain professionals, such as my developmental physical therapists who are

able to look at angles of neck extension and postural sort of markers that then can go on and be representative of children at risk for certain developmental disorders, including ASD.

Dr. Insel: Okay. We're going get quickly around because we are holding space for Zach to make final comments here. So we haven't -- so we'll get to you.

Idil?

Dr. Wall: This is Dennis. I have a comment from the phone, but I could make it later. I don't know what's going on in the room.

Dr. Insel: Okay. Thanks for joining. Good.

Idil?

Dr. Wall: No, I've been on. I'm raising my hand, but nobody can see me because --

Dr. Insel: Ah, okay. We were looking, but we can't see you all that clearly. So just hang in there, and you'll come next. Idil is going to make a comment.

Dr. Wall: All right.

Ms. Abdull: Hi. I wanted just to make the comment that you have said, Dr. Insel, that where are we now? So in terms of a lot of people are saying we can identify autism in 12 months or 18 months, but that's not what's happening on the ground.

So children are not in majority being diagnosed with autism at 12 months, and so we're failing if we say and we translate that to the community. And then that's even for mainstream children. For children of color, minorities, low income, and that would be the tools that are effective, I don't think we have any tools, unless maybe Amy Wetherby can update us on that.

But I would like to see what are the tools that are available now that can go into the community so that because we know autism is about behavior, and behavior is about culture, and cultures are different, what tools are available so that these children that we know have been -- that have been

getting diagnosed years later, how do we catch them? How do we catch the children who are now in disparity?

Dr. Insel: Amy?

Dr. Wetherby: Yeah, so excellent point. So I think -- I think it's not just having the screening tools, but it's a process of gathering information from multiple sources, triaging, putting it together, and then who's going to make the diagnosis?

So I think the biggest challenges are -- so we do have a new set of very promising tools that we've begun to apply across cultures in very low-resource settings. And we have very good relationships between the parent report and the observational measures. So it's very exciting.

But I just see then this stumbling block from who's going to make the diagnosis? And no one wants to do that in the community. Pediatricians don't want to do it. Certainly developmental pediatricians are, but there are so few of them. And then the early-

intervention system doesn't want to.

And so we need to figure out a way to form a partnership of the primary care and the early-intervention system together. They could hold hands together and do this. And I believe that both, together, have the pieces, but we need to put them together in the community to make this work and reach the families that you're talking about.

So the diagnosis is -- we haven't really talked about that, but that's -- an important piece of this. And then treatment, if we can show that the treatment is effective early, then more and more doctors will see the point of diagnosing early.

So I think we've got to link it all up. It's not just screening, but it's screening that's leading to who's going to make the diagnosis, and then we're going to want to do that if we have early treatment that's available, that's community viable.

Dr. Insel: I think Dennis had a comment on the phone. Yeah.

Dr. Wall: Yes. You know, at this point, I'm really going to be echoing essentially that same -- that same point -- and actually the point made by Joe Buxbaum and by Paul Wang, which is that I think we've come a long way with development of tools that have sensitivity and specificity north of 80 percent, and we're still not diagnosing children at the ages where we could be.

And I think that comes down to deployment and implementation. And Amy's comments are perfect. That is that, you know, we have to start to figure out how to operationalize the process of screening to diagnosis and how to involve diagnosing physicians in the process in ways that are more ubiquitously deployed across the country.

And so I think, you know, energy and funding need to be focused there, that if we can -- if our objective is to drive down the average age of diagnosis, we can -- look to what we have in the armamentarium of tools

that have been developed and actually start to figure out how to deploy them in more ubiquitous ways.

Dr. Insel: You guys have just written the one-page report here. I mean, this is really very, very helpful. And I guess, John, you'll be the actual scribe for this. So I hope you're capturing this because that's really very useful.

Carlos, Geri, and then Zach.

Dr. Pardo: Actually, my comment is from adult neurology. I think when you see an adult patient, you have a lot of targets. When you see a child, you see basically a moving target. So brain development is critical. So between 0 and 12 months of age, we see a lot of neurological changes.

So I need to confess that I'm a little bit a skeptic about establishing screening and diagnostic tests in the first 12 months of life, particularly from clinical point of view because we are exposed to a lot of variability and a lot of changes in the brain

from motor, language, behavioral, et cetera.

So I think that what has been done with Baby Sibs has been very valuable. I wonder if we need to pay more emphasis on issues related with the community samples because we probably may learn more from those samples in the future.

And again, a note of caution is having an app is fantastic, but I think that the evaluation process needs to be quite exhaustive before introducing something that may be misguiding diagnosis or treatment.

Dr. Insel: Geri Dawson?

Dr. Geraldine Dawson: Good morning, everyone. Just a few quick comments. In terms of your question about sensitivity and specificity and being able to detect autism before the syndrome is fully manifest, I think it's important at this point to distinguish between below 12 months and the answer to that question versus, say, 12 to 18 months. And I think you're going to get two very different answers.

And because I think that we're doing much better at 12 to 18 months and versus below 12 months, most of the work so far really has come out of the infant sib work, and it's been really exciting and there are actually multiple markers that have been showing up that will predict which children as a group -- not necessarily on the individual level -- but as a group will develop autism. But those have not been validated at the individual level, which they would need to be.

And secondly, they haven't been studied in the general population. So we really don't know how they would work there.

The second is to really distinguish between risk and diagnosis. So those are completely different things, and I agree that it's going to be very hard at this point to diagnose autism before 12 months and that we really need to be thinking about risk.

The second point is that we really have focused mostly on genetics and behavior,

things like visual attention, which are really important. But I think we also need to broaden our early risk markers to look at a number of physiological markers, such as sleep and EEG and autonomic measures and GI function. And I think we may really, by adding that breadth, add a more full picture of early risk.

And then, finally, in terms of service delivery, I think one of the most important points to come out of the early studies, such as Karen's, is that when families receive a positive screen. So in your study, for example, only 60 percent of those families actually then sought out a diagnosis.

And so there is a huge gap between families hearing that the child may be at risk for autism and their engagement with services. And we need to really understand what are the factors that could promote family engagement, particularly in low-resource and diverse populations.

Mr. Robison: Where is that 60 percent

from?

Dr. Dawson: In Karen Pierce's study.

Dr. Insel: Karen's study. Yeah, this is the San Diego pediatrician effort. Yeah, great point.

Zach, you finally are going to get to sum this up because we're at the end of our timeframe.

Dr. Warren: No pressure. No pressure.

I'm going to echo a lot of what Geri just said at this point. You know, I think when we're talking about infancy, we're not yet at a point where we've gotten to be able to identify individual, actionable risk markers, nor have we effectively thought about methods for combining biological and behavioral markers in a way that would lead toward action.

We're getting closer toward sort of being able to implement screening processes of meaning and action between 12 and 24 months, but there are remaining concerns about the measures that we have. We're

currently working on this AHRQ review of population-based screening instruments that we'll put to the U.S. Preventive Task Force. In fact, we'd love to have information about sensitivity, specificity, and negative predictive value on a population level.

We're left with being able to talk about truly positive predictive value because we haven't funded studies to really follow this through in population samples, right? We're really talking about clinical identification samples, small samples. That lack of information is one of the major factors that's impacting uptake of these screeners into common practice.

It's not that clinicians wouldn't be utilizing screeners that had these properties that could really, truly, accurately identify. And so I think, you know, we are limited to basically general development on our screener, the ASQ, the Infant-Toddler Checklist, and the M-CHAT at this point, which are self-report methodologies for

attempting to identify autism on a population level.

Almost all of those methodologies really rely on parents to report an impairment, right? So it really talks to are we really doing this before these impairments are manifest? Or are we actually saying not only does it have to be manifest, but we have to have a parent concern about that manifestation in order to lead toward action, right?

So I would just put some caution out there in saying that, yes, I feel like we can identify autism accurately in expert teams between 12 and 24 months, but we could probably do that for an overwhelming majority of those children. We do not have the capacity or the tools to realize that on the community level, and we haven't been funding some of the work around screeners or sort of the uptake of screeners within community practice to really drive that as fast as we would like to.

Dr. Insel: Okay. Well, we're at the end of the time allotted for this question. It doesn't mean that we've solved all the problems. So I do -- we're going to have to move on because we'll run out of time on other questions.

There will be further opportunities, though, for feedback. I must say the process here I thought was going to be mostly a debate, but I'm struck by how much consensus there is about where we are and what we need.

And John, as you write this up, and you'll get lots of help from people around the table, the other piece that would be great to reflect is what we've actually accomplished. So where were we in 2008, and where are we today? And it does sound like there's been, at least for Baby Sibs, very significant progress. But the real challenge now is to convert that to community samples and to know how to deploy.

So I think we've heard a very, to me, consistent picture of what the need is, but

also a sense that we've come a long ways in the last few years. And certainly, the paper in *Nature* of the mommies group last week helps to demonstrate that.

Dr. Boyle: Can I say one last thing?

Dr. Insel: It has to be brief Coleen, and then we've got to move on.

Dr. Boyle: Yes, yes. So the one thing we didn't talk about, and we will put it in the notes -- and it's actually for the first objective -- was the fact that we don't have existing tools for diagnosis. We talked about diagnosing young children, but we don't really have this efficient, you know, low-cost tool to be able to do diagnosis. A lot of work on screening, but not a lot of work related to diagnosis.

Dr. Insel: Yeah, it's a good point. And John, I think when you write this up, Geri's comment about distinguishing risk from diagnosis will be a really vital issue to clarify where we've made progress and where we haven't. So that's helpful.

We're going to go on to Question 2. This is, I think, all day you'll see we're going to be fighting the clock because I know there's lots to talk about.

So you can see on this one, "How can I understand what is happening?" The aspirational goal is "to discover how ASD affects development, which will lead to targeted and personalized interventions." Who's the person assigned to write up the final report from Question 2?

Dr. Insel: Walter Koroshetz. So Walter, you want to take us through this? And because really what we're here to do is to help you, so let us know your sense of what's come out of the discussion so far.

Dr. Susan Daniels: Well, maybe I could start, since I know Walter wasn't able to join us for part of the call? You were there for the whole call?

Okay. So, well, we have some bullets here put together. Maybe I'll just start off with Question 2 "How can I understand what is

happening?" The aspirational goal is "discover how ASD affects development, which will lead to targeted and personalized interventions." So this is the big picture, overall goal for this question.

And these are some of the key points that were shared on the last call: the need to further define key research questions in the study of ASD and immune and metabolic mechanisms, the need for more genotype/phenotype studies, the need for more longitudinal studies, the need for increased supply of brain tissue and other tissues for post mortem studies and appropriate technologies, the need for larger clinical studies, and the need to standardize data collection.

And so those are just some brief bullets of things that came out of the call. There is more detail in the handouts that you have. But then, you know, I'll turn it over to Walter to talk about what we -- what we discussed.

Dr. Koroshetz: Yes. So I think Carlos is here, and Lyn and Alison are here from Question 2. Anyone else?

Okay. So, so this -- I guess we discussed what have we learned in the last number of years with regard to the biological basis of autism? And so it's a big question. It's got many, many components. I think, in general, we've made a lot of progress in understanding because we really didn't know much in 2008, and there has been a lot.

But there are so many different areas in this -- in this question, some of which we haven't learned anything about. So I guess that's the thing. It's kind of a potpourri of areas. So let me just go through some of them.

One of the first areas we talked about was the relationship between fever, metabolic abnormalities in the immune system, and the central nervous system that might influence ASD during prenatal, postnatal life. So in this area, we have learned some things about

some areas, particularly the immune system becoming more important with the identification of gene pathways and brain tissue from persons with autism and the differences to typically developed -- and the differences seen versus -- typically developed. And it puts the immune system in the front and center.

There have been studies and animal models of immune challenge during pregnancy in animals and showed behavioral and developmental changes, which are very kind of interesting in terms of the syndrome we see in humans and the potential for either environmental or infectious or autoimmune challenges to the mother during pregnancy as a potential cause.

In terms of things like fever, we really haven't really learned too much about fever. There is – it has been brought up by many parents that the children actually do better during an elevated temperature. This was an area where, you know, it's in this group. We

learned a lot, but that's an area that seems to be open.

With regard to oxidative stress and disorders of mitochondria in autism, again, there's a lot of information out there, but it's really hard to understand what it means in a composite way. And so there was a recommendation from the Group that it may be a worthwhile kind of regrouping -- get a whole group of people who study oxidative stress together in terms of what are the techniques -- how could they be applied to autism?

And similarly with mitochondrial genetics, we've learned a lot. There was a workshop when I first came. The question is -- but there were certainly limitations that were easily realized for moving this forward into autism research -- the question is, have any of those challenges been -- been broken -- so that we can kind of move forward again?

With respect to the issue of neurodevelopment in females with ASD, there

have been some studies that have more recently been coming on, looking at this area. There have been certainly some genetic studies that show, for instance, with copy-number variant effects that are relative to gender. But we thought that we needed larger sample sizes to understand the genetics and the brain imaging and the developmental patterns and how they differ between males and females.

With regard to the issue, the next issue on our list was awareness among the autism spectrum community of the potential for brain and tissue donation. So this is a very specific item. We believe there has been made -- a lot of progress been made -- the Autism BrainNet, a bigger outreach to let people understand how important this is.

But on the other hand, we also recognize that the number of brains that are available is still grossly below what's needed. So although there has been outreach, we still need to push this because it's thought to be

a really acute need in the field for brain tissue for people to study.

With regard to the genetic conditions that allow us to understand biological pathways, I think that's probably the area in which there's been the greatest progress. A lot of what we know about the biology of neurodevelopment in ASD comes from particularly either genetic defects that lead to a syndromic condition or some of the linkage studies that are associated with a nonsyndromic autism that have led to this general hypothesis that there is something wrong at the synaptic level, given many of the mutations kind of point in that direction.

And those have led to a couple of interventions that are in trials, and you know, I think it's a very -- we have to be careful about false expectations. The issues with many of these genetic discoveries and the identification of molecular pathways has to do with how robust they are, how well they

generalize across the autism spectrum, and then the process of going from that to a therapy is very difficult, as it will be in autism as it is for any disease.

In terms of co-occurring conditions, the issue of familial autoimmunity was brought up as an important one to pursue. But that the tact may be that we need to look in actually the clinical populations that have autoimmunity, look at autism there, as opposed to looking for -- only looking at -- familial autoimmunity in people who are diagnosed as autistic.

Understanding the biology mechanisms for elopement and wandering. I don't think we -- we were not able to come up with anything under that subtopic.

In terms of sleep, there have been numerous descriptive studies in the last 5 years pointing out the sleep disorders and characterized them in one small study of melatonin as a potential treatment.

With regard to regression, I would maybe

ask some of the others to kind of talk about this issue. On the call, the issue was that we have to be -- we have to really look at this carefully, that we need longitudinal studies to track this and that it's still an important area to concentrate on as it might show a link between a trigger and a falling off of function.

Let's see. With respect to the longitudinal studies that comprehensively examine development over time, we thought that this was happening. But there is still -- I guess one sense was that there are -- very few that really have the depth and scope of what was intended, which was a kind of going through autism over the lifespan and concentrating on all the transition points from fetus to infant, infant to child, child to adolescent, adolescent to adult, young adult to middle age, and middle age to elderly.

So we haven't really kind of done all of that. We have longitudinal studies which are

ongoing, but there's still a lot to do.

Response to the biological signature findings of discovery for performing diagnosis, risk assessment -- there is a lot going on in this area, particularly in the imaging area and then looking at connectivity in autism. So this is, again, a tool that may be developing but requires really validation.

There was an interesting study where all the autism groups got together and looked at their functional-imaging results and did kind of a really multisite sensitivity/specificity analysis on functional imaging, and that's the kind of work that needs to continue.

So those were my summary notes from our discussion going through the multiple areas, but I'd be interested maybe if Alison or Lyn would make some comments, or Carlos?

Ms. Redwood: Thank you, Walter. That was a wonderful summary.

One of the things that I seem to notice in looking over the literature is that a lot of these findings seem to occur in silos. For

example, again, I'm going to be a broken record here, but the immune findings, the metabolic findings, the oxidative stress, the mitochondrial abnormalities.

And I think it would be important to take these findings and use sort of a systems biology approach to be able to identify some common underlying pathways or mechanisms because, you know, it seems as though these can be self-perpetuating in -- let's say, an environmental toxicant can lead to immune dysfunction or some of these metabolic abnormalities and derangements that we're seeing.

So if we really look at this a little bit more broadly and then bring in also the genetic piece and combine that with these pathways to see what genes are controlling those pathways, I think that's going to be a way to sort of advance the information that we have now.

Dr. Pardo: I think that the potential role of the immune system is -- in the past

several ideas have been evaluated in some detail in autism spectrum disorder, and I think that we have learned a lot. And I think that one of the most important issues is that we understand that autism is not an autoimmune disorder, as some people claim many years ago.

But obviously we recognize the immune system may play a role in some pathogenic pathway, and particularly because it's important to understand the immune system is part of homeostasis and brain development. And obviously, any disruption of the immune system is going to be important.

I think that in the contributions, taking a look at accounting for what has been learned on this issue in the past several years is the role of maternal vitamins, maternal immunity, and the potential role of maternal infection both from animal models and from epidemiological studies.

I think that we still need to learn a lot, particularly in community studies,

because, for example, the role of maternal infection and potential immunotoxicants during pregnancy are critical and very important for understanding disruption of brain development. So I think that in the future probably we may need to pay more attention to that.

The studies of maternal autoimmunity actually are quite interesting. It's not necessarily that that is a common denominator in autism, but it appeared that a subset of patients with autism have been exposed to some type of maternal autoimmunity. The work of UC-Davis and Judy Van de Water actually are very interesting on this issue.

But the other aspect that broadly we may need to pay more attention is how the immune system is overlapping with genetic factors because there is a lot of function between genes associated with the nervous system and genes associated with immune function, and many of them may overlap. And I think that future studies on animal models, in vitro

models, and actually in humans probably should address that gap in knowledge.

One thing that is very interesting is the recent understanding how the gastrointestinal system will relate to immune reaction in babies. Our immune system is designed by the GI track in the first days of life.

So in the future, probably studies of microbiomes of the babies and understanding how the microbiome and the microbiota of those babies influence development of the immune system, and eventually, the interaction with the brain are going to be critical to see how the influence between the environment and brain development.
And I think that we need to pay attention to that because the animal models in the past few months have shown a quite amazing amount of information about that interaction and brain function. I'll stop here.

Dr. Insel: So before we open this up, if I can just, again, make an overriding comment

here? I think what the report that we're going to construct here will have to do is to the extent we can remember or say this is what we knew in 2008, this is what we know today. So what did we think was true then that we've now proven to be false? That would be really helpful to know. What did we not know then that we know now that maybe is ready to generalize or to take to the next level?

So I want to really -- because there are lots of new opportunities, no question about that. And we'll hear about lots of things that are happening that we can now study going forward.

But I just need to remind you, this is really an accounting exercise of the last 5 years. So we want to capture for the -- in this case what -- $362 million that we spent on trying to answer this question, what did we get? What did we find out that we didn't know in 2008 when we started?

Joe?

Dr. Buxbaum: I think you might have just warned me off about what I was about to say. But, and this will come up, I think, a lot in Question 3. I do think there's progress on certain associations, environmental or otherwise, and maternal autoimmunity is one. We now have the tools to figure out the direction of that association, and I think that is the logical next step.

But I think there are epidemiological and molecular ways of saying, okay, there's autoimmunity and there's autism. Is that a causal relationship, a reactive, or independent relationship?

And I feel that with all of the advances in these kinds of other findings, associations that are environmental and otherwise, we are now in the stage to actually understand the direction of that relationship before we assume that it's definitely from the environmental finding to the autism. Because if it's not you're wasting a lot of time on models that are

probably not valuable.

Dr. Insel: Karen?

Dr. Pierce: Yeah. I think one interesting point for discussion that I haven't heard raised is, you know, many years ago, several researchers discovered the phenomena of early brain overgrowth in autism, and I haven't really heard that readdressed here.

Also, looking at the report, I didn't notice there have been several post mortem studies who have shown using blinded methods. So, for example, brain slides are sent out to scientists who do neuron counts who are blind to the diagnosis of the subjects, and then numbers are retrieved and then split into diagnostic groups that show an increase in neuron numbers. But the neuron sizes are smaller.

So I think what's really interesting is that that might be a reason for the variability that you might find in various head circumference or MRI studies regarding

brain overgrowth in autism. But using blinded stereological counts, we are seeing an increase in neuron numbers. And I think that's important to this Question, particularly as it relates to timing, because, you know, neurogenesis occurs prenatally.

And so, theoretically, the reason -- one of the reasons -- if it's true -- that kids with autism have too many neurons is this insult is happening prenatally. So it's giving us a little bit of a timestamp.

And our group has done that. It's also been studied by Patrick Hof's group and also found increase in neuron numbers. So I think this concept of early brain overgrowth is important and fundamental to the biology of autism.

Dr. Insel: Good. Anshu?

Dr. Batra: Tom, I'm curious if anyone at the table can comment. Have there been any studies looking at the population of, let's say, the IVF population and the risk factors

or development of autism, as well as the prematurity population?

And again, when we say prematurity, it's so dependent on what level. Was it 32 weeks, 28 weeks, 24 weeks? And that's really going to dictate the level of developmental delays, of neurodevelopmental delays you see.

Dr. Insel: Coleen, is that -- do you want to respond to that in terms of prematurity?

Dr. Boyle: Well, I was hoping Julie -- Julie, you want to talk about that?

Dr. Julie Daniels: No, go ahead.

Dr. Boyle: I mean, preterm birth is clearly a risk factor. I mean, it's one of the strongest risk factors for autism or at least the one that continues to hold up within -- as data accumulates.

Dr. Julie Daniels: Ten percent risk.

Dr. Boyle: Yeah, a 10 percent risk. IVF, I don't know. So Julie, you might want -- do you know the recent on that?

Dr. Julie Daniels: There isn't anything

that's really been done yet to really look at that very strategically. I think we're planning to look at that and see. But there hasn't been anything that's really been rigorously evaluating that hypothesis.

I just want to make a comment with regard to the preterm birth. I think we have this tendency to look at things like preterm birth as risk factors in a causal way that some component of being preterm actually leads to autism. But I want to caution against only looking at it in that manner because I think there's some shared etiologies that might be important to consider, and I just don't want to overlook that component.

Dr. Insel: Joe?

Dr. Buxbaum: There is a *JAMA* paper that just came out on IVF that shows that most IVF is safe, and the one that may be associated with increased risk is the most when you have non-motile sperm, and you're doing sperm aspiration. And there again, one can ask

about the causal direction. Is it the IVF causing autism, or is it the fact that you have sperm that's very, very disrupted that increases the risk for both?

And I think for preterm birth, we are at the stage right now where we can actually do the study and ask whether preterm birth causes autism or whether there's a shared risk for both. That's an easy study to do with modern methodology.

Dr. Insel: So again, I want to push us on the specific question of since 2008, when we think about the biology of this, this condition of autism, what do we know now that we didn't know then? We have a list of needs up here. That list, I'm sure, can get longer and longer. But it would really be helpful for this report to frame it that way.

Geri?

Dr. Dawson: Well, I'd just like to put one finding on the table that I think was really important was the work that came out of the infant brain imaging study that showed

changes in the development of white matter based on diffusion tensor imaging analysis of 6- to 12-month-old infants who later developed autism. So that we did not know before, and I do think that that's a really important breakthrough in terms of understanding both the underlying biology, as well as understanding potential risk factors before onset of full syndrome.

Dr. Insel: Great. And there are other hands. We'll go around this way this time. Idil?

Ms. Abdull: In terms of what do we know now and what from the last few years, do we know why some children -- and I speak as someone who hasn't slept since my son was diagnosed with autism more than 5 hours -- do we know -- I sleep when I come here -- do we know why?

The sleep issue was -- even before autism, he wasn't sleeping. So do we know why some children are just not sleeping? Is that a precursor to them getting ASD later on?

And then also what do we know about why some children are just minimally verbal or not verbal? Do we know anything or research that said why some children are just not talking?

Dr. Insel: Does anybody have an answer to this? Is that, again, really searching for what the discoveries that have been made in the last 5 years relevant. So I don't -- does anybody have an answer?

Nancy, are you -- or Karen?

Dr. Pierce: I mean, I don't necessarily have an answer, but there have been some imaging studies published with infants with autism between 12 and 48 months and have shown that the infants that have the most language impairment have the most degree of hypoactivity in the superior temporal gyrus, which is a part of the brain that's really key to language.

So what's kind of nice is that you can actually use functional brain imaging to look at correlations with behavior, and what we're

trying to do is also then maybe link that to prognosis. So if you're seeing a baby who's not talking very much, they have hypoactivity in the superior temporal gyrus. Is that going to help us predict where they're going to be when they get into preschool, for example?

I think that's a really important area of research, and it's exciting for us is that imaging actually really works functionally. And you know, you'd expect abnormalities in the superior temporal gyrus because that's the part of the brain that helps us talk and -- or helps us process language -- and in fact you do see that. So we have a paper with Eyler on that, and we have an inter-hemispheric correlation with [inaudible comment] showing particular deficits in the superior temporal gyrus.

Dr. Insel: And Mukherjee and colleagues at UCSF have shown that kids with autism -- not in terms of function, but in terms of actual structure and the number of connections between brain areas -- have a

disconnection, relative disconnection, between amygdala and the fusiform area, the area that's important for social and face processing.

So some of that's emerging, but it's -- it still needs to be validated, replicated.

All right. Geri, then Alison.

Dr. Dawson: Just really briefly, I think consistent with that, a few months ago, our group published a biomarker that you could examine at age 2 using electrophysiology. So this was ERPs to known and unknown words. And what we find in normal brain development is, as children acquire language between 12 and 18 months of age, you see cortical specialization for speech with a focal ERP from the left hemisphere.

And we were able to predict which children would go on to develop language and as measured at age 6 using this ERP measure at age 2, and those who did not develop language were those children who showed a very diffuse pattern of ERP and did not show

this focal left temporal response to known and unknown words. That was in PLOS a few months ago.

Dr. Insel: Great. Okay. Alison?

Ms. Singer: So I think another thing that has changed in what we've known since 2008 is really the way we're looking at gender differences and the differences in the ratio of diagnosis. I think we used to look at the 4-to-1 boys-to-girls ratio and say maybe there's something testosterone linked that causes boys to be more affected by autism.

But now because of a lot of the genetics work that we've done and the fact that we're seeing copy-number variations in the girls as well, I think there's more thinking that maybe there is some protective factor that the girls are able to utilize. And maybe if we can explore this further, it's something that would lead to a protective factor that could be employed for all individuals.

So I think that's a real shift. I think

another shift in thinking since 2008 with regard to brain is the way we think about how entrenched brain cells are. I think we used to look at learning disability and some of the disabilities as if certain neurons -- if certain systems didn't come online by certain times, by age 3 or by age 5, we used to think if people didn't -- if children didn't -- have language by age 5 that they would never be able to develop language.

I think we've seen through some of the intervention studies that the brain is more malleable. And through some of the medication trials, we've seen that we can actually reverse the core symptoms of autism through targeted interventions. And that is a real shift. I think we used to think that if these systems didn't develop, that those pathways atrophied and could no longer be accessed.

So I think we should think about when we write up the -- and I will help you write up the chapter, Walter, including those changes just in thinking.

Dr. Insel: Scott?

Dr. Robertson: So one comment related to what I had noticed on that one objective. Well, there are a couple of comments I had, one shorter on the female/male differences. Is it possible also -- maybe this relates back to Question 1 more -- is that are we also still missing some groups?

I mean, I know that there's a search for the differences that are genetic or biological-wise between females and males because that's been kind of the expectation that there's something there. But is it also still possible that we're just missing a diagnosis? Maybe just because it presents differently, we're also just not diagnosing enough females?

What I just also wondered on a broader question, have we learned anything more on what happens early on and why that's different as the individual gets older? For instance, in the sleep area, where maybe I'm misunderstanding in the literature, but my

understanding of what I had read recently is that a lot of the sleep differences are much more -- have a bigger impact in early childhood -- and that kind of tails off as individuals get older into adolescence and adult life.

So why is that a case? Why is there a larger impact, for instance, on sleep? Why are there maybe larger differences seen in early childhood versus later on in adolescence and adulthood? So kind of linking back some of the things you see later on in development with what we're learning in early childhood is something that I was wondering where we've kind of learned more in that area.

Dr. Insel: Yeah, Nancy?

Dr. Minshew: I think with regard to sleep problems, I believe Valerie Hu at George Washington University has reported a number of circadian rhythm gene CNVs, and they cluster in the low-language group. So those papers have been published, and there

was also some finding about some of the CNVs resulted in an enhanced impact of testosterone on brain development.

So speaking to the idea of why are there more males than females being the influence of testosterone on brain development itself and different CNVs resulting in enhanced impact.

Dr. Insel: Anshu?

Dr. Batra: I just wanted to comment on the gender issue. I mean, I think that in general neurodevelopmental disorders are more common in males than females. So I think that, you know, why should autism be any different? I mean, we see essentially the same types of ratios.

And so again, clearly there may be some differences as these individuals develop and as they go through certain developmental periods like puberty, and there, the hormones might cause some shifting or changing in either the improvement or, you know, worsening of symptoms. But overall, you know,

again, as a developmental pediatrician, yeah, I do see more males than females in general in my practice. And so --

Dr. Insel: Lyn?

Ms. Redwood: Tom, getting back to the question of what have we learned since 2008, having served on the Committee since that time, one of the things that I notice is that it seems as though we're starting to look not just at the brain, but also at the body.

And I know in 2008 I brought up a comment about children having gastrointestinal problems. And for you that served on the Committee at that time, that was -- resulted in some very robust conversations. And so it's amazing now to see that we're talking about the microbiome. We're talking about GI. We're talking about immune abnormalities, metabolic abnormalities.

So I think that's really been sort of a see change, that we're starting to look now at the body as well as the brain, and that's

also reflected in the literature as well. When you do literature searches, you see that the research on, say, theory of mind have really dropped, and there's been a lot more research on these physiological abnormalities.

And I think it's just such a really ripe area for research, and I'm glad that the IACC is looking at those issues now, too, and I think that that's a big difference from 2008 that I wanted to bring up.

Dr. Insel: A question that we'll want to grapple with at some point is whether this Plan had any impact on that shift. I don't know if it did, but it's still --

Ms. Redwood: One other thing I just wanted to say really quick about sleep is that if you remember the presentation from Dr. Buie with a lot of the problems with reflux and a lot of the behaviors that we see in children that when some of these, you know, underlying medical conditions like GI were addressed, the behaviors also changed,

and also sleep patterns improved. So that may be another underlying mechanism with sleep.

Dr. Insel: Joe?

Dr. Buxbaum: Just to get back to the CNV question. So the largest study to date under review, I think, with the Autism Genome Project says that females are much more likely to have a highly pathogenic CNV or a CNV disruptive with an FMR1 target than males.

So I think we are at the point now where there are some protective factors in females, and it needs to be overridden almost by more genetic loading, at least in the case of the CNV studies. So I think that is progress.

Dr. Insel: Okay. Carlos? And I want to also ask people on the phone after Carlos so we can get your input as well.

Dr. Pardo: Just talking about advances in the past 3 years, one of the questions 3 years ago was the potential role of microglia, potential manipulation of microglia as immunological factor in autism,

and studies from Sue Swedo here at NIMH in a small group of patients have shown that manipulated microglia with medications like minocycline do not have any effect in behavior.

And that is important to point out because it was believed that microglia may have been the bad actor of the immune system in the brain, and actually, in the past 3 or 4 years, we are learning more and more about the beneficial effect and the normal biological function that microglia have on synaptic plasticity and synaptic formation.

And I want to point out this issue because it's extremely important for brain development and plasticity, that manipulating the immune system with medication probably is not the best avenue for management of autism.

Dr. Insel: So those on the phone, and any comments or anything to add? The question on the table is what have we learned since 2008-2009 about the biology of autism?

Dani?

Dr. Fallin: I think one of the things that we have already hashed today that we've learned in the last 5 years really is the pointing to earlier and earlier time points of understanding the origins and really to the prenatal period. And with that in mind and covering lots of different things going on, if we think about mechanism and understanding mechanism, then maternal-fetal interactions must be critical to that understanding.

And so thinking about what we will say when we get to the parts of what we think what we do in the future. So I know that's not what you asked us to do now. But I think what's critically relevant to what's happened the past 5 years is realizing that we probably shouldn't just be looking at understanding mechanism in the child alone, but understanding that maternal-fetal interaction and, therefore, mom and child mechanisms. Both from the genetics and other aspects.

Dr. Insel: Walter, is this helpful?

Dr. Koroshetz: Okay, Dr. Insel: Yeah.

Dr. Buxbaum: I think that we've learned that it's etiologically much more complicated than we thought it was.

[Laughter]

Dr. Insel: We were so much younger -- older than -- or younger than that now.

So what I'm hearing from this conversation is that one of the things that's happened a lot in the last 5 years is sort of deconstructing autism. As you've talked about the biology, it's the biology of the immune system, biology of sleep, biology of maternal-fetal interaction. It's a bunch of things that are not autism writ large, but maybe what we're trying to do here is to understand the component parts and then be able to put it back together. And maybe that's where most of the progress is.

And I think it's very helpful, as Carlos mentioned, to also identify the studies that have been done that tell us some things that

we were very interested in 2008 are probably not going to be fruitful. So that we -- even if they're not published, it's good to the extent we can in this report to include negative findings so we can help the field to veer in a different direction.

As Lyn mentioned, there really are shifts that are taking place, and we need to be part of leading that instead of just following it.

Walter?

Dr. Koroshetz: Yeah, just back to Lyn's point that when you deconstruct something, the danger is that you can have a million little pieces going on and you don't actually see the big picture. People get focused on their one little pathway, and you know, how generalizable these findings are becomes the big question after a while.

And also you have to be really careful about false expectations based on what's been discovered in one segment, having people start thinking that, oh, you know, I can

treat all my kids with anti-inflammatory agents if there's inflammation. Immunity is important in autism.

You know, as Carlos mentioned, that could really backfire because the knowledge is not complete and because it hasn't been tested in a reliable fashion. So I would go with Lyn's point about trying to -- we should always be trying to -- think about how to put the systems back together from all the little pieces that are out there.

Dr. Insel: There was a comment on the phone?

Dr. Hertz-Picciotto: Yeah. Hi. Irva Hertz-Picciotto. I wanted to second whoever the speaker was talking about the maternal-fetal interface as being really critical. And in light of that, I wanted to also bring up I don't think anybody has mentioned on this topic the maternal nutritional factors and some of the work from our team suggesting that maternal folic acid intake in the periconception period might have a protective

effect in terms of autism risk.

And I think it's really sort of amazing, again, within the last 5 years there have been several papers now, including a replication from a prospective study that came up with almost the exact same degree of protection of about 40 percent. And I think that brings up from the point of view of the biology the issue of epigenetics and the potential role of that very early embryonic period where methylation patterns on the embryo undergo some really major changes, including basically stripping of the methyl groups and then reestablishment of those, of the methylone, and the potential role that that may play.

Probably not just in autism. This may not be a specific mechanism, and I think that may be true for many of these other areas, both the immunology, the metabolic, the oxidative stress pathways. I think many of these may have -- they may have -- implications, though, for autism and other

neurodevelopmental disorders because they are so basic to brain function and structure and development.

Dr. Insel: Okay. I think, Nancy, I think you'll have the last word.

Dr. Minshew: Okay. I think one area that we've made substantial progress in is appreciating and developing measurements of alterations in connectivity. Geri talked about being able to look at focal -- or local cortical specialization by 2 years of age as an index. And certainly, we're also seeing more sophisticated methods for looking at connectivity. But importantly, both Geri and across the age span, you can change those cortical systems connectivity with intervention, which I think has been very powerful, and we'll see more payout from that.

But we wouldn't have conceived of that, you know, 5 years ago necessarily. But I think that's very important.

Dr. Insel: Last -- any other last

comments? Anshu?

Dr. Batra: Tom, I wanted to comment. That was a really good point, Nancy. As I think about how I practiced 5 years ago and how I practice now and what I share with my families, I have to say I think 5 years ago, even though I'm a very positive person, I always, you know -- I always impart "let's see how far we can get" to my families.

I have to say 5 years ago, I think I probably had more of a ceiling in terms of progress and expectations for the kiddos that I saw. I think now I think I'm a lot more positive with families. You know, for me, I think I focus -- I don't focus as much on the age of the child that comes in as I used to. Oh my gosh, earlier the better.

Early intervention is key, and yes, it is. Because, you know, the earlier you capture a child, the earlier -- the less bad behavior that you have to undo to then establish good behavior. So you just have less that you have to redo.

So yeah, I think that in 2013, I think the issues of neuroplasticity and the issues of some of the other things we've talked about, I think that has really shed a more positive light on, you know, where we can go with our kids.

Dr. Insel: Nancy?

Dr. Pelphrey: Tom?

Dr. Insel: Yes, someone on the phone?

Dr. Pelphrey: Hi. This is Kevin. I wanted to echo some of the things Nancy said, what Alison Singer said, and what Geri said and add to it with a sort of -- even I think that since 2008, we've developed an understanding across the field of brain imaging, of what the neural systems phenotype of autism looks like.

We've got a sense that it's not as set as we had imagined, that even though autism is a neurodevelopmental disorder, there are preserved systems that through behavioral and drug intervention can be recovered to some degree and to a surprising degree, both in

terms of local specializations and in the connectivity. And those studies are agnostics underlying pathophysiological mechanism.

We're starting to learn that we can treat autism at the neural systems level and see changes that predict behavioral changes. So that sort of revolutionizes our level of hope but also our treatment outcomes. So instead of looking for gross behavioral differences, we can look for early indicators of treatment outcome, treatment success in the brain, knowing that like every other neurodevelopmental disorder, we're going to see changes in the brain prior to the onset of behavior, but also when we treat, we'll see changes in the brain prior to changes in behavior.

And so that makes me much more hopeful. And sort of combining that with what we're learning about potential compensatory processes in girls and unaffected siblings and what we're learning about how many infant siblings at risk show brain risk but don't

develop the behavioral symptoms, I think that there's really extraordinary hope around what we can do with imaging at this point to inform how we treat autism.

Dr. Insel: Okay. We're going to have to finish up. I want two more comments, one from Nancy, and Lyn, you're going to get the last word.

Dr. Minshew: Okay. I think what I would add to this, as carrying on with what Kevin said, is -- and the RDoC approach -- is that we're finding that as we do a more neural-systems-based intervention that the interventions that we are developing for autism are going -- are generalizing -- to having an impact on related disorders.

The other thing I would say is that molecular-based, molecular pathway-based treatments are coming, and that's substantial progress. Because we can do a lot with new interventions coming along, whether it's infants or adults, but we really need the less severely affected.

For the very severely affected, I think their recourse is going to be these molecular-pathway-based interventions. And there's been a lot done to promote that kind of research to begin looking at the role of glia as a support for neurons, and might there because there but also capacity for intervention. So tremendous advances have occurred.

Dr. Insel: Very hopeful. Lyn, last comment.

Ms. Redwood: Okay. One of the things that I see as incredibly positive is that we are now embracing the fact that recovery is a potential. Back in 2008 I made a comment about my son having recovered and was -- that's not possible -- was the thinking at that time.

And now we are seeing recovery, and what -- something like in 30 percent -- we're seeing these children have lower intellectual disability than we saw back in 2008. So I really do think that there is progress and

there is hope, and we should never give up.

Dr. Insel: That's a great way to end. But before we break, I just want to check in with Walter to see if there's anything else you need from us?

Dr. Koroshetz: No, I think the comments are great. I think what we need is feedback as we put things together and make sure we have the kind of points that people want in there.

Dr. Insel: Great discussion. Let's take a 10-minute break, and we'll reconvene at 5 till.

(Break)

Dr. Insel: Okay, so let’s reconvene. I - I don’t have a gavel, But we need to have everybody back to the table if we're going to stay on schedule. You've been really good so far about staying within our timeframe. So I want to make sure we don't get a late start for Question 3.

It's great to see so much interaction from the Committee and the experts, but I

need to have everybody back to the table so we can begin Question 3.

So we're going to move on to "What caused this to happen, and can it be prevented?" And I'm going to ask Cindy Lawler to take us through where we've come so far with the first two meetings, and then we'll want everybody to give some input into again this question of where were we in 2008? Where are we today?

Dr. Lawler: Good morning. And I'm going to do things a little bit differently. We have 15 objectives under Question 3, so rather than go through each one of them and summarize, I'm going to make some general comments that reflect the discussions in the first two calls because I want to preserve the maximal time for input from experts and other IACC members that are around the table.

I think, overall, what we heard is progress has been mixed. Certainly if we just look at whether we met budget recommendations, in most of the objectives,

they were met at least partially, if not fully. But of course, that doesn't tell the whole story.

I believe we have made some really stunning progress in the area of autism genetics. This has come over the past 5 years not from the GWASs or the candidate gene approaches, but really from the sequencing studies, recognizing the role of copy-number variants and, more recently, the single nucleotide variations or single point mutations.

There is still, I think, a lot of work that's needed to understand the -- and link that structural variation in a causal way to autism. We know in many cases those structural variations are not unique to autism. I'll turn to my autism genetics experts in few minutes to fill in a little bit more around there.

We have made good progress in the area of epigenomics if you just look at the number of studies in the budget. But that's a case

that's misleading. There has, I think, been very little advance in the idea of environmental regulation of epigenomics, although this is really critical because this provides that bridge that could link genes and environment and autism etiology.

In the area of environmental risks, I think we have made some progress. Air pollution, I believe, is an instructive example. We now have about six or seven studies demonstrating an association, you know, higher risk with exposure.

This is unlikely to be the smoking gun, and it's not because it's going to be probably a primary risk factor, but really more likely reflects the ease of measuring that exposure. We are -- studies are leveraging large investments in air monitoring by EPA, and there are ways to get proxy measures of exposure just by asking simple questions about residential history and doing land regression and mapping where you live relative to major roadways.

So that really is instructive because it, you know, if you think about how much further along we might be if we had better ways to measure lots of the other exposures that I think are real candidates. And this points to a challenge that we have in measuring reliably, accurately particular exposures, particularly in the relevant time period.

And we certainly need more attention to apply new analytic approaches that are coming out of this growing field of exposure science to help us analyze multiple, you know, chemicals, for instance, and very small volumes of biologic samples to begin to understand whether there are persistent biological response indicators that one could measure that could tie back to prior exposures.

And a related point is the value of studies that enable prospective collection of exposure information during early periods of development.

Another point, we need to capitalize on the use of nonhuman models to explore gene-environment interaction --

Dr. Insel: Excuse me for a moment, Cindy.

If you're on the phone, could you make sure you're muted? Hello? We're hearing some background conversation. It would be good to mute your phone if you're listening in.

[Laughter]

Dr. Insel: Thank you.

Dr. Lawler: Perfect. Lots more opportunities in the microbiome. I think another message that I heard loud and clear, particularly on the last call, and if you look over the aims or the objectives under this question, there's a lot of overlap in those aims, and there are multiple studies that we're funding that are relevant to more than one objective, not surprisingly. And this really, I think, reflects the richness and the opportunity that we have to examine new hypotheses, really making use of

infrastructure that we've now funded. SEED, CHARGE, MARBLES are three studies that come to mind, and there was a very strong sentiment that we need to continue the investment.

In some cases, the primary investment to date has been in the infrastructure, and now we have lots of banked specimens, you know, lots of very rich data that's being collected. And the next step would be to fully capitalize not only on those large autism-centric studies, but really to continue to look for other large population-based studies where we could embed an autism component.

And I think the last point that I'll make: When we had a bit of a discussion about the aspirational goal, the feeling was, yes, causes are being discovered in many -- for autism. In many cases, the findings are not yet ready for translation to clinical practice or public health, and the real need is to further cultivate the investments that

we've already made.

So those are my just umbrella thoughts from the last two calls, and I'll just open it up to others that were on those calls, other experts in the room, and IACC members.

Dr. Insel: Comments. Matt?

Dr. Carey: One brief one, and I think you covered it a little bit, was -- one thing we saw a lot in this was kind of I don't want to say alarming but, you know, a definite trend of fewer projects over years. Projects, you know, while funding levels may say one thing, the trend of number of projects is going down.

And I think that's something we really don't want to happen. As you said, we want to make sure -- we invested the money in the infrastructure. We want to make sure we reap what we want from that, and we also want to make sure that other new projects come online with this.

Dr. Insel: Scott?

Dr. Robertson: So can folks address how

and seeing on the objectives --

Dr. Insel: So just before we get to -- because I just want to make sure that the people who were on the call or who constructed this so far have a chance to weigh in. Any other comments from people who are part of this Group?

Okay, sorry. Go ahead, Scott.

Dr. Robertson: Okay.

Dr. Insel: I didn't see your hand. I'm sorry. Go ahead. Okay. Well, you'll get in there.

Dr. Robertson: I'll try not to talk too long. Can folks address the large gap that we're still seeing in particularly on enrolling racially and ethnically diverse populations in the research?

I mean, when I look at the objective here where it says only spending $188,000 on that over what we were projecting, out of $3.3 million, that's a pretty large gap on that. And yet it doesn't seem to mesh a lot of the research that showed a lot of health

disparities in diverse populations.

So I'm not understanding, you know, why -- is there a reason why -- for this question why this is the case? Is there anything we can move forward on that to improve upon in this area?

Because that gives me large, really, really large concern in terms of seeing that gap on the funding, even though it's been emphasized a lot that we need more research in that area under the understanding on ethnic and racial and socioeconomic status differences among diverse population groups in science?

Dr. Lawler: Thanks for pointing that out, Scott, and I omitted that. That was a real gap that was identified, and not only just trying to understand how exposures may differ along racial and ethnic lines, but other subgroups as well that may show vulnerability, whether that be, you know, comparison of girls versus boys or geography or some others, the clinical groupings.

How to look at exposure, heterogeneity, and how it impacts risk is key, and we have not done a good job of doing that to date.

Dr. Fallin: So I agree, and I'll come back to why I think that may be. But I would emphasize, though, that some of the studies and things that have been mentioned in other aspects besides that question actually are quite racially diverse in their recruitment.

So SEED, for example, I don't know what our numbers are, but it's got to be 30-ish percent, maybe even higher than that that's nonmajority. And I can't speak to models that everyone's mentioned, but I'm guessing to the extent that for several of our sites -- and certainly I think in some of the other studies that I've seen -- there are even Spanish translations of every aspect of the study.

So there really are different minority groups that are being included in these studies, although it didn't fall under that particular subquestion. But to get back to

your point, the reason that it's probably still true is it's already expensive enough to do this well and with the right rigor. It takes a different and creative strategy to capture underserved populations. And that is often even more expensive, right?

So I think -- yes, but paying attention to that and infusing that and acknowledging that it takes a creative and different and potentially expensive strategy would be very important.

Dr. Hertz-Picciotto: Can everybody hear me now?

Dr. Insel: We can hear you.

Dr. Hertz-Picciotto: Hello? Oh, okay. Sorry. This is Irva. There was a problem. I had to get the coordinator to help.

I actually wanted to talk a little bit about the disparities question and also some of the other general issues we discussed this week. With regard to disparities, we did -- actually, one of the discussion points earlier this week was to -- there was a sense

that that dollar amount may be -- might or might not reflect efforts in this area.

And in particular, the investments that Cindy talked about have been in some studies that are -- that may well have diverse populations, and so there was a suggestion that some effort be made to try to put together what the figures are in terms of the enrollment, particularly in these -- you know, these studies oriented toward the genetics and the environment in terms of what the racial and ethnic distributions are, as well as the socioeconomic representation in those studies.

And I think there was some issue as to whether there were resources to be able to do that, but many of the studies are in large metropolitan areas that do have diverse populations. Our CHARGE study in California actually is about one-third Hispanic and probably another 15 percent other racial/ethnic groups. So probably somewhere close to 40 or 45 percent that are nonwhite,

non-Hispanic.

Dr. Insel: So I'm sorry to interrupt, but since we have so limited time, I want to make sure, since this is a question about etiology, and we're now talking about diversity --

Dr. Hertz-Picciotto: Yes, I was going to move to that.

Dr. Insel: -- is there any evidence from the last 5 years that the etiology is different depending on racial/ethnic group? Is that -- is that how we got here, or is it just a -- sorry?

Dr. Hertz-Picciotto: I don't know that's been addressed, and I think the genetics people could speak to that. May I just talk about -- maybe switch over to another issue here, which is in terms of what we do know about etiologic factors and potential etiologic factors. I'm actually pretty encouraged by the progress that's been made in the last 5 years where, and part of that is because 5 years ago, we knew almost

nothing.

So you know, there was a vast place to go, and I think what's been exciting is that the number of clues that has emerged in these last 5 years is far higher than maybe I might have expected given, you know, maybe fairly modest investment.

And you know, this includes besides -- Cindy mentioned air pollution -- but there've been studies on pesticides. There are the studies on maternal metabolic conditions, studies on maternal fever and infection, studies on prenatal exposures to some of the medications, SSRIs being one suggesting potentially increased risk.

The nutrition, which I mentioned earlier under as we were talking about Number 2, and that includes both prenatal vitamins and then some recent work on fatty acids, omega-3s, for example. Back to the chemical arena, there are several studies now suggesting that phthalates potentially play a role in some of the social affect measures.

So the growing number of clues, sort of the, I don't know, low-hanging fruit that may be out there is encouraging. But I think the really big challenge is, you know, for one thing, validation and further studies. But perhaps more importantly is linking that to some of the mechanisms of action and really understanding to what extent modifications in these factors might actually change risk for child development of autism or severity of symptoms.

And you know mechanistic areas of immunologic aberrations, epigenetics, metabolism, and so forth. So I think -- and linking the gene and environment fields, which I think, unfortunately, has really operated very independently of each other, and I think that new technologies in epigenetics and gene expression and copy-number variants, doing de novo copy number, which seems to, again, suggest that interaction of genes and environment is really an area where we have lots of

opportunities to move.

Dr. Insel: Irva, that's very helpful. You know, I wonder if we could get you maybe working with Cindy to summarize in a way that comes down to a single number or a single indicator of where we are now relative to where we were 5 years ago in understanding all those environmental factors.

Like how much of the risk did they predict? How do they aggregate? What's the effect size? I think what we'll need for this report is just some indicator of progress, knowing that we're not there, but we're trying to give the public a sense of, after investing $340 million or $380 million here, what do we have to show for it?

So to the extent that you can help us with those kinds of numbers, that would be great. To the extent that we can, we want to be very quantitative about where our progress is. So we'll ask you to work with Cindy on that.

Lyn, you've had your hand up, and I

missed it before. So let's go back to you.

Ms. Redwood: Well, it sort of goes along with what Irva was just saying about environmental toxicants, and I do think we've made a lot of progress. There was a really nice review of research trends that was published just this last year in *Molecular Psychiatry*.

And when they looked at environmental toxicants, they identified 190 publications that investigated environmental toxicants and ASD, and 170 of those implicated a relationship, which was like 89 percent. And of those, 19 implicated lead, 25 implicated mercury, 8 implicated other metals, 18 implicated exposures to pesticides and other pollutants, and 4 implicated dietary toxicants.

So I think what we need to do is to look at this list and look at what's come up in the literature and validate it and see if we've gotten to the level where we can actually take some action and try to either

influence public policy in investigating these chemicals further, whether it's BPA or some of the known bad players that we have already, and trying to do preventive efforts in terms of reducing exposures. I think we're at that point. So that was one of the things I was wanting to mention.

And also that there has been a tremendous amount of research in this particular question focused around genetics, and when you -- and I hate to do this, but I'm going to have to do it -- but when you compare the investments looking at environmental factors, they just are not as robust, and we're very concerned that one of the long-term studies, the EARLI study, is no longer being funded.

So we're seeing sort of this downward trend that I think really needs to be addressed and that we need to make sure that epigenetics and environmental research are continuing to move along at the same pace in terms of the funding. So those were just the

sort of two comments from a particular question that stood out.

Dr. Minshew: I think one of the major advances in this toxic epidemiology work is showing that the exposures of greatest concern are prenatal, during pregnancy. And if that's correct, I think the public ought to have a great deal of less angst about a lot of things that they used to have a lot of angst about.

But I think that's a major advance to have gotten to the point where we can say it's not all of these or these time periods. It is the intrauterine time period that we're most interested in, which links to the maternal-fetal relationship comments that were made earlier. But I think that, in and of itself, is a major contribution.

Dr. Insel: Joe?

Dr. Buxbaum: So three very quick related points. One is I think an obvious area of success has been the move from understanding that there is a genetic etiology or component

to autism to reducing that to specific genes and loci in a way that has really been quite dramatic and driven by a lot of the new technology. And I think it's to the NIH's credit that they recognized that that was an opportunity and leveraged that opportunity.

In terms of representation of minorities in genetic studies, that's still -- or underserved population generally -- that's still a real problem. And I don't think there's any evidence that there are different etiologies by ancestry, but there's good evidence that with the right ancestry, you get more power to find genes, right, with admixture mapping and so on.

And so, I think there's both kind of -- you know, there are multiple reasons to kind of focus on that and to enhance it as well.

Dr. Insel: So you had mentioned before as well that there's been real progress. Again, can we make that quantitative? What -- what do we have in hand today that we didn't have 5 years ago?

Dr. Buxbaum: So I think we have, you know, using the new unbiased methods, we have something between 7 and 10 new genes, but 120 genes where at least half of them are real, right? Maybe even a higher number. And the data for that, the kind of statistical data is strong, and we'll be able to resolve those 120 pretty quickly down to 60 new genes.

And I think that we are making genetic findings now in about 30 percent of kids.

Dr. Veenstra-Vanderweele: So I would say, even extending on that, the model for how genetics contributes in autism spectrum disorder has changed, and it's something that's changed pretty dramatically. If you look at this document, the expectation was that GWASs -- that association studies -- were going to have this huge impact.

And what's happened instead is rare, but very robust risk factors that are identified in a large portion of the population, something we wouldn't necessarily have predicted. It was a large investment, but I

think this is an area where you'd say the yield has really been quite incredible.

Dr. Buxbaum: Just a follow-up. I'm sorry. It's right in front of me. One of the things that came up on the phone call was that the transition from GWASs or SNP-based mentality to rare variant mentality did come with a higher price tag; there is no question about it. But as you pointed out, all the findings that have been made have been in that ladder approach.

Dr. Insel: That is a completely different understanding of the genetic architecture than where we were in 2008. Coleen?

Dr. Boyle: I think one of the major, I guess, achievements -- in many ways, this one is hard to quantify -- but that is the investments that we have made in infrastructure, particularly for population-level studies. So we're right now at the cusp of being able to -- and as Irva has just eloquently told us about many of the risk

factors that have been identified through her work and others' work around the table -- we'll be able to look at those in more detail.

We'll be able to look at those based on phenotype, as well as phenotype and genotype relationship at a population level. So some of that's sort of hard to quantify, but I do feel like we're at -- these investments have taken years, the 5 years, to actually develop. Some of the people around the table know this. We're really going to be able to look at much more depth.

I don't think we can answer what you just asked about, you know, how these risk factors predict risk yet or what proportion, but I think that in the next 5 years perhaps we will be because we'll be able to replicate. We'll be able to drill down much deeper on that.

Dr. Insel: But in the way that Joe described the genomic, the state of genomics, are we -- can we do that for the exposome or

for these environmental factors? I think one of the things that's hanging us up here when we talk about the environmental factors is it's very wishy-washy. It's very hard to get clear numbers about what the impact is on any given factor, whereas people need that in some way.

And especially if we've made a huge progress, and I think it was great the way Irva has that list of factors that we weren't talking about 5 years ago that we know today. It'd be really helpful to get some understanding of where the effect sizes would be there and how to think about them.

Idil?

Ms. Abdull: I was just going to ask a question in terms of if I look at this -- and I feel like a little fish in the Indian Ocean being just a mom with all the scientists here -- but if I look at it as just regular mom, just regular street, what caused this to have been, and can it be prevented? So in the community -- and parents are asking that --

in the Somali community, they're asking that. In other communities, they're asking is it my genes? Is it the environment? Is it where I live?

So what, what would the experts say to that? If a parent comes in, and they have four children with autism, not one or two. In our families, it's four, what -- something is happening.

So I would like to see what are you going to tell the people who are listening and the people who are just living on regular streets what caused this to happen, and how can I prevent it so my, you know, next child doesn't get it?

Dr. Insel: Jim? You're going to answer that question?

[Laughter]

Dr. James Perrin: I certainly wish I could. It's a tremendously important question and one that we would love to be able to answer. I would just sort of ask a couple questions, though.

One is I think this great work on toxicants and the exposome is tremendously important. We have learned a lot about epigenetics in the last 5 years. And I'm sort of hoping that many of these studies are really linking the exposures to very high-quality epigenetic research and the ability to understand exactly the mechanisms by which these exposures may be important.

I might just add that the American Academy of Pediatrics has taken epigenetics as one of its primary policy areas to be understanding at this stage and the implications of that.

My other quick question is really where does this fit with the National Children's Study and its efforts to get reinitiated and going again? And how can that be useful in this context as well?

Dr. Insel: There are a lot more questions than answers around the table, and I'm still waiting to see someone answer Idil. But maybe we can come back to that.

Geri?

Dr. Dawson: So I think one of the really important advances over the last 5 years that has come from genetics is the development of animal models for autism. And so when you think about the animal models that we can create now with SHANK genes or neurexin or others, where we now are able for the first time to understand the pathophysiology and think about drug discovery because of being able to create those animal models and looking for convergence across those animals models.

And I know at least a couple of projects now where they're using comparisons across various genetic animal models of how different compounds influence pathways in either common or different ways as a strategy for understanding, you know, common -- commonly affected -- pathways and idiopathic autism. So you know, that's a huge breakthrough, and it's something that I think gives us a toehold in autism that a lot of

other neuropsychiatric disorders don't have.

Dr. Insel: And there was a poster yesterday at the Society for Neuroscience -- or Wednesday -- on 23 different models being compared in just that way. So there's a lot going on.

Dan?

Mr. Dan Hall: Yeah, I just wanted to mention that I guess where we've come in the last 5 years is that we now have 8,000 exomes available and shared for the entire autism research community, and we expect that to double in the next 18 months. And so, you know, as this data is there and available, the ability to do computation and get these alterations from various genomic pipelines with software and bringing it all back where we could see the differences and verify the 60 alterations that are out there is going to become a reality.

And on top of that, we're looking at the ability, since we're linked with IAN now, the ability to allow parents to go in, provide

consent, to give their consent to share where they lived at time of birth. We can pinpoint the geolocation, and so it's absolutely possible to take these 20,000 exomes or in the next 5 years and link that with location.

And on top of that, get all the environmental air quality, pollution, building material-type information. So you know, I couldn't -- I couldn't resist because this is more of a Question 7 issue. But since the topic has been coming up.

Dr. Insel: Yes, Julie?

Dr. Julie Daniels: So as far as thinking about accomplishments, one thing that I think feels better now than it did 5 or 6 years ago is this appreciation for the complexity of the etiology of autism and that we're not just looking at genes or just fishing for some environmental exposure. But there's a greater appreciation for how these in working together to really figure this out.

And echoing Coleen, now we have finally arrived at this infrastructure with which the

same study we have both genes and environmental exposures measured, and I think that that's something that we're just now getting our hands on and have a lot of promise to sort of milk over the next few years.

Dr. Insel: So this goes to Jim's comment about the National Children's Study. We'll come back to infrastructure with Question 7 later in the day because I think this is really an important piece of answering Question 3, just getting that in place.

Go ahead.

Dr. Julie Daniels: Yeah, thanks. And then, just like one more point on that is that this idea that we will be able to identify a cause, I think we kind of know that it's this constellation of events that must occur. But I don't think we are communicating that as it goes back to something that was mentioned this morning about what the expectation should be as far as what we can do on a certain short

timescale to quantify a cause for any given gene or any given environmental exposure.

And I think it's really this genetic susceptibility to exposures or these interactions that are going to have sort of small effects when you look at them in a population, but really large effects when you really identify the susceptible subgroups. And I think that that willingness to accept that philosophy, I think has come around over the last few years.

Dr. Insel: So again, something for Cindy to try to capture in the write-up because I think there's, as many people have said, it's going to be important to frame progress in a particular way. So some of it will be technical. Some of it will be conceptual and helping people to understand how the thinking in the field is shifting.

Let's go to Dani and then to Nancy, and I see -- and Matt and then Joe.

Dr. Fallin: So I think highlighting the advances in genetics is important and shows a

good use of money spent. I think in this question about the balance of the two and how you even summarize progress and one versus the other, we have to acknowledge just partly that infrastructure point that there was a lot of built infrastructure around understanding GWASs, understanding sequencing, understanding analysis of all things in between that had occurred before 5 years ago or right at that cusp then.

That we're sort of starting that kind of infrastructure in the exposome and environment question world now. And the other challenge that I face, trained as a genetic epidemiologist who now does environment and epigenetics work, is that we were lulled into this idea with genetics that we can measure your DNA at any time and understand the sort of context of that. I can't measure an environment at any time in your life and know the right context, particularly if environments in the perinatal window are the most important.

And epigenetics is also potentially incredibly important, both as a mechanism or even just as a useful biomarker, but timing matters there as well. And so I think, unfortunately, what that means is we have to do new recruitment and new kinds of studies and prospective studies that we didn't have to do in the same way to get really great advances in genetics.

And so I think we should balance the importance of what we've learned in the genetics but realize that it will probably be harder and that we'll have to balance those kinds of efforts in that way. So I just wanted to say that.

Dr. Insel: Nancy?

Dr. Minshew: I had two comments. The first is that when it comes to environment, I think it's important to realize that the most potent influence is a positive one postnatally, and that's the role of human interactions. So that we've heard again and again about how interventions can make a huge

difference, whether it's early infant or it's during the school years, the preschool programs where it's a very good quality program with a great leader and it doesn't matter so much the specific program. They're getting good results.

Or it's the impact of peers, training a peer. You see that in mice but also in children that peers can be a powerful mediator. So I think that's a really important emphasis and one where parents could have training about what is good -- what are social interactions? What are positive ones? What are negative ones? And what can they do?

Because ultimately we're talking about autism, but there are a lot of developmental disabilities, so to speak, that arise that will have social, emotional, communication consequences that parents can address if we could establish in the first year and all subsequent years and during school milestones for what is good social interactions? What

are those milestones? What should the K through 12 people be promoting for social communication, problem-solving, etiquette?

The last point I had was about how do we track exposures? And although it's politically loaded, it seems to me an easy way is almost everybody has a cell phone. Whether you're very poor or just poor or whatever country you live in, they have cell phones. And if you had permission and a great programmer, you could track where that mother has been.

You can't track what she's eaten, but if she had to buy it, you could track it, so to speak. So that is one way to get directly at where did they live, where did they go, how long did they spend? And with the right programming software, whatnot, you could do that.

Dr. Insel: So that would go into the new opportunities space. So yeah, go ahead.

Dr. Borges: I just wanted to add that to look at the other side of the exposure,

thinking about susceptibility, kind of bringing it back to the individual. It would be more in the line of mechanistic studies probably, thinking of what triggers because, of course, not all children that are exposed develop the disorder.

So and that goes back to what was said before in terms of guiding us to potential therapies, for instance, and I could anticipate that those triggers are -- if we can identify them, will probably be different for different groups of children with autism. And that could even help us identify subtypes, too.

So I'm just thinking -- going back to the individual.

Dr. Insel: Right. So this may turn out to be another one of those cross-cutting themes that we'll want to capture.

Matt, you had your hand up?

Dr. Carey: Thanks. Let me put out actually two ideas. One I kind of added after I raised my hand listening to Dani, and it

probably ties into what she was saying. But I think if we look at genetics, we say that there have been great successes with that, then the lesson from that is if you fund it, you get results, right?

I mean, and you know, we could fund -- you know, it is time to put a lot of money into environmental. I mean, we will get results if we put the money in there. I think we could take that learning and do that.

I remember when we were doing this exercise last year and Isaac Pessah was talking, and we just -- there had just been some really good things that came out like weeks before we talked. And he was just chomping at the bit, saying, yes, genetics guys have given us the things we can actually really chase down and work on. And he was very excited about that.

But you know, we need to put that investment in. So I think that's got to be a lesson we learn from that.

Another one I would sort of say -- when

we just look at the genetic part of it, we talk -- we had a lot of discussion about how the understanding has changed in the past 5 years since the Plan was first written. I think the understanding has changed, but the sort of the structure of the Plan hasn't.

And the way I would say is we need to be able to group now. If the single genes are easy to group. You could say, okay, you've got this gene. You've got that gene. We can group people together and start feeding into Question 4 and start feeding into therapies and everything else.

When we have lots of other things, then it becomes much more difficult to group things together and say what are the subgroups of autism based on these genes? And I don't know if that's really covered in here and how that will get covered in the future.

I remember talking to one neurologist who talked about, you know, this very exciting genetic condition which has a high risk for autism, and he was very excited

about it. And I said, well, you know, how about you've been doing this and this and this research institution for a long time, how about grouping them together? He said, "Oh, that's impossible. I've got 5 or 10 people in 20 years. I've seen 5 or 10 kids in 20 years I've seen with this condition. How would I be able to put together any kind of a study and feedback?"

But I think, you know, if we look at all of these as individual CNVs and individual SNPs and everything else, there will never be the impetus to kind of group people together and make an impact on all those kids. So I don't know how to do that, but --

Dr. Insel: Joe, you have the answer to that.

[Laughter]

Dr. Buxbaum: Oh, do I? Well, sure, I can touch on that. That wasn't why I raised my hand, but I do think that there has been some good investment in putting things together in the genetic sphere, and I think that, you

know, by virtue of these various interactomes and gene expression kind of technology, where you can create unbiased networks in the brain, there is a very kind of kind of natural, I would say, next step to use unbiased gene discovery plus unbiased kind of network molecular pathway building to understand how genes coalesce into subgroups.

And I think that we're in the position of being able to do that in the next couple of years. So I think that I think the genomic revolution extends now into transcriptomics and proteomics and things like that, and that allows you to kind of take hundreds of genetic findings or other molecular findings and put them into pathways.

I think we're doing -- I think that's, I think, maybe counts in the win column at least where we have the infrastructure and the tools, and the resources, I think, to do that at this point in time.

But what I was really going to say --

[Laughter]

Dr. Buxbaum: -- was thinking about, you know, prognosis and treatment. I mean, there is something to be said, following Geri's comment, about that gene discovery leads to natural model systems that have construct validity. They've also led to targeted therapeutics, obviously, that the Seaside trial is one of them, but there are other ones as well.

And these are the first time we can point to neurobiologically driven clinical trials, and I think there is definitely some activity in the Seaside trial that everybody acknowledges. And there are other such trials in other subtypes of autism, and they're also being tried in nonsubtypes of autism. And they got some major change.

I think the idea that we're actually doing clinical trials where you can say, hey, there's a rationale behind this, I mean, obviously, in the behavioral domain, that's been true for years. But in the pharmacological domain, it's simply been

absent.

It also goes to, I think, prognosis because if there's a molecular finding in the family, in the old days it was just if there was fragile X in the family, you could talk about recurrence. Now there are many findings on the X chromosome and other parts of the genome where the family can learn something, right?

They can learn particularly about recurrence, sometimes about surveillance. And that, too, is a sea change I think that we just didn't have a couple of -- even just a few short years ago.

And I guess the final thing I wanted to mention is that there is a mapping of environment now to mechanisms, at least in the case of paternal -- or parental age, right? There have been two studies, one that just on many sites have now shown that increased parental age, particularly paternal age, is associated with greater de novo mutations that seem to mediate some of that

risk. But there's at least one study or two that show that actually there are epigenetic changes that probably also contribute to that increased parental age and autism risk.

So I think we're mapping kind of robust environmental findings to mechanistic findings, and I think that's a huge thing that we couldn't have said even a couple of years ago.

Dr. Insel: Scott and then Anshu, and then we're going to wrap up.

Dr. Robertson: Yeah, I just wanted to just dovetail a little bit with what Nancy had mentioned about connecting with what we're learning about early development back toward support for families and parents and others for being able to help for knowledge resources and supports, for social development and communication, executive functioning, et cetera.

And I think it's kind of one of those dramatic ironies kind of things that we had decades ago -- we had the really -- I mean,

it wasn't based ever on any science, but that false belief that there was something psychogenetic in parents with the whole refrigerator parenting thing from decades ago. And the irony on that is that some of the studies that I've seen have suggested that parents play a supportive role.

The better parental support, better family support, it can help with outcomes in terms of long-term development and what the individuals are able to achieve in their lives. And I think we need to do a better job of connecting some of what we're learning here back toward what we can -- what parents can actually be doing practically.

What other family members, how maybe siblings -- not just looking for siblings for how autism is shared genetically and biologically, but also looking at siblings, how siblings can be supportive individuals as they're growing up and can help with some challenges that are happening.

So I think we need to connect that

better to -- as I say, for -- what parents and families can actually be practically doing with individuals as autistic kids are growing up and going through childhood into adolescence and adult life.

Dr. Insel: Great. Anshu, last comment.

Dr. Batra: Well, that puts a lot of pressure on me. Last comment.

I guess I was just thinking about this from a clinical standpoint, just really boiling it down to how has it been different for me 5 years ago and how is it different now? And you know, the positive side is we have a microarray test now. I definitely am checking that more, as opposed to 5 years ago. It was super expensive 5 years ago, and insurance companies didn't cover it, and so that's a positive.

I still don't know what to do with them. Most of the time, it comes back either normal or, well, you know, you got some copy-number variants, and we don't really -- it's unclear, unclear clinical significance. So

that leaves me with, you know, well, I don't know. I guess I have to wait another 5 years to figure out what this means.

And then the other thing I think -- it's something that Nancy and Julie had mentioned -- was I think I am taking more of an active interest in the mommies who bring in their kids who have -- who have ASD or other neurodevelopmental disorders. And when I find out they're pregnant or they are thinking about adding to their family, I think I'm spending more time in counseling them about some environmental and nutritional and dietary factors than I probably wasn't doing 5 years ago as much. So --

Dr. Insel: That's a good discussion. Let me just throw a few things on the table before we wrap up, and this is really for Cindy because I think there are some things we haven't talked about, which are striking to me because I think this is an area where 10 years from now we'll be in a very different place. And we'll look back and

think why didn't we see it in 2013 when it was already there?

So there are a number of opportunities that have already been explored with; for instance, we haven't talked about iPS cells or stem cells as a way of looking at mechanism of disease, which is already beginning to play out for syndromic autism, where we've been able to see mechanisms that do separate the neuronal differentiation in people who have those kinds of mutations.

But it does seem to me that some of the major breakthroughs are probably in tools and techniques or observations that never have the word "autism" connected to them, and some of the most important investments of the last 5 years have been around projects that are going to revolutionize how we do this work but don't really ever mention autism in the process.

So just three quick things that I think are going to change the world in this field. One being the observation that in the

developing brain, that is, in the fetal brain at the very time when Nancy and others have said we should be most focused, the patterns of gene expression in the brain are completely different than they are after birth. So much so that many people who do molecular neuroanatomy would say that that fetal brain is like a different organ altogether. It needs to be understood in a different way.

So there have been several very large, you know, $30-million and more investments in mapping that. That's all now available online free of charge through the Allen Institute, a project called BrainSpan, and will be absolutely transformative for people who want to study autism and how it develops.

Second observation is that we've talked a lot about epigenetics, and it's now clear that the epigenetic modifiers and how they act in the brain are completely different than they are in other tissues. The actual targets for both methylation and for histone

modifications are not the same in the brain as they are in blood or skin or anyplace else we look, and that means we have to begin looking eventually in brain itself to understand what the environment is going to be doing in development or thereafter.

And the third and perhaps most concerning for what we've been doing is observation just from the last few weeks that the genome in the brain is not the same genome that you find in blood cells and the possibility that there are lots of large de novo variations or somatic variations in the brain that can be localized just in one circuit or one lineage or even one set of cells that you'll never pick up by doing this in lymphoblasts or in peripheral cells.

We don't know if that's the case in autism, but my goodness, it does say that there could be, and since we've already heard a lot about CNVs and spontaneous mutations in autism that are found in blood, you'd certainly think that they may also be found

in other tissues, including brain. And that has not even been investigated.

So those could be -- those are three areas that I think we now appreciate that we didn't know anything about 5 years ago. In fact, in truth, we didn't know anything about any of this 1 year ago. So it's really all very, very recent but could be really transformative going forward.

Last comment before we move on is I know there has been concern about the balance, and we've heard this around how we've invested at least in Government, but also I think in the private sector as well, between genomics and environmental studies. And I think a lot of that is driven simply by where you think you have the most traction, where the results are coming from, where you're getting the most progress.

As Matt says, it's a little bit circular because you tend to also get the best progress where you make the biggest investments. But scientists want to go where

they can move quickly and where they have progress.

It's interesting to note, I looked at this just for this meeting because I thought this might come up, that if you look at other parts of the NIH portfolio, areas where we know a lot about the environmental factors -- so lung cancer or peptic ulcer disease, and you can go down the list. Actually, there is an even greater proportion of current funding is in genetics than what we do in autism today.

And the reason for that is really important to know. It's not just because it's easier to do genetic studies than other kinds of studies. It's that in the genetic studies, as you've heard a little bit from Joe and others, it's our best window into the mechanisms of disease. So it's not as if we're specifically using all of that money to find out what you inherited and who to -- you know -- where this came from.

But as with lung cancer and as with

peptic ulcer disease and as with other diseases that we know about that have both a genetic and environmental component, the genetics right now is giving us this amazing insight into mechanisms and into sort of the biological underpinnings and the complexity. And that's where a lot of the work is going.

Putting that together with what we're learning about the genetic patterns of brain development is finally beginning to, I think, really give us enormous progress, much of this just in the last 6 months and some of it just in the last 3 months. And some of it actually not even published, a lot of it not even published.

So this is a time of extraordinary progress in this area. I think we'll look back and see it maybe a little more clearly in retrospect than we can now because it's all happening so quickly. But I hope that the report will capture some of this so that it's not simply pointing to all the things we don't know, but recognizing that relative to

2008, wow, I mean, there has been a lot invested, but there's an enormous amount that we have learned that we had no idea about even, frankly, in 2012. And that's really good to know.

Dr. Buxbaum: I'll help with that write-up.

Dr. Insel: Yeah, anybody else who wants to contribute? Geri?

Dr. Dawson: So Tom, would you also include, in terms of just general advances in methodology, the connectome, and has the connectome had any particular findings that haven't -- implications for autism that we should be aware of?

Dr. Insel: Yeah. The connectome is this large, again, $35-million investment in doing 1,200 individuals, 300 twins, but all selected because they're healthy, sort of to get a reference atlas for the wiring diagram of the human brain. I don't think it's there yet. This is really going to give us the methods we'll need.

We've just done a supplement to begin to do this in children so that we can begin to then take this to autism. But we're probably about 3 years away. But that will be the next 5 years that will be done.

But that's another example of a big investment that's being made to provide the tools we need to make progress on the imaging, and just like we have a reference genomic atlas, we'll have a reference connectomic or neuroanatomic atlas. Okay.

Dr. Koroshetz: There is -- there is a pediatric brain imaging study being run out of San Diego including development of white matter over time. Anders Dale is running it. It's pretty high level, and I would think that that would have the most immediate implications.

I mean, the biggest problem that I see in this whole field is that this technology can be abused very easily because it's very hard to standardize, and there's a lot of dial-twisting that gives you these maps. And

what they mean, I think we have to be really, really careful. The validation is going to be incredibly important.

Dr. Insel: Okay. I'm mindful of the time. We're a little bit past where we wanted to be. There's a lot to talk about, but we are ready for public comment. And I want to make sure that we don't invade that part of the agenda.

So if everybody's okay with that, we'll wrap this up at this point. Cindy, I hope you got what you needed. But as you heard, there are people volunteering to help on the writeup.

Dr. Lawler: I have volumes to condense.

Dr. Insel: Okay. Good.

Dr. Lawler: And I would appreciate -- Joe, thank you for offering, and I'll circulate it to others who may have an interest in reviewing it.

Dr. Insel: Okay. I think you can be very upbeat. I've got lots of notes, too, which I can share with you.

Let's go on to public comment. We have several people who had written in. Let me remind you that there are both written and oral comments in your packages. So I want each of you to make sure you've had a chance to look at those if you hadn't seen them before the meeting.

And we will hear from each of the people, many of whom have traveled to share their insights with us. Given the time, I'm going to have to restrict each public commenter to 5 minutes, and we will start with Megan Davenhall.

And I guess what would be easiest, you can either come to the table or you want to -- Susan, are you going to -- or you want to use the podium? Okay. Is the podium mike on?

Megan, can you just tap the mike, and let's make sure it's on. Good. We can hear you.

Ms. Davenhall: Hi. Thank you for having me here.

My name is Megan Davenhall. I won't be

presenting my public comment, but that of my colleague, friend, and fellow autism mother, Lisa Joyce Goes, who could not be here. So thank you for allowing me to present this in her absence.

“Good morning. My name is Lisa Joyce Goes. I am coauthor of *The Thinking Moms’ Revolution Book*, cofounder of The Thinking Moms’ Revolution Social Thought Movement, and contributing editor to the *Age of Autism*, and a human rights panelist for the Academy of Excellence in Learning in the south suburbs of Chicago.

Most importantly, I am a wife and mom to three kids, one of whom suffers the tragic effects of iatrogenic -- sorry, iatrogenic autism. My friend Megan is here today, like many of my colleagues, to deliver testimony about my son, Noah Patrick Goes. But unlike them, she will be sharing his life from the perspective of my father-in-law.

Unorthodox, I know. His observations need to be documented for public record so

that the American citizens may be privy to all the reality of iatrogenic autism and how it directly impacts our society and culture.

As a deacon in our community, my father-in-law was tasked with the job of writing a homily about what it means to be a true disciple -- a man of honor and integrity who puts the welfare of others before himself and truly serves his fellow man in the present. After thoughtful reflection, he decided to speak about our dear family friend, the good Dr. Andrew Wakefield.

Dr. Andy has been instrumental in helping us find proper medical care for our son Noah, who, upon receiving the correct diagnosis of autistic enteritis and esophagitis and receiving appropriate gastrointestinal care for his illness, was finally potty trained in a matter of weeks.

This normal milestone for most families experienced during the toddler years came with much celebration in ours. Not because we were a household that no longer had to pay

the monthly cost of diapers, but also because after 6 long years of searching for answers to the painful, yellow, grainy, hot liquid that would pour from our son's bowels at times 20 times a day, leaving large, raised, painful rashes in their wake, we finally had a real diagnosis that led to viable treatment, rather than the repeatedly documented, untreated, and ignored toddler diarrhea associated with autism.

So along with my immediate family, my parents and in-laws journeyed with us through Noah's treatment and grew to know the good Dr. Andy quite well. Now I knew the huge risk my father-in-law took deciding to speak about Dr. Wakefield in this manner. I asked him repeatedly if this was something he really wanted to address from the pulpit. But he stood firm, knowing Dr. Andy would be a man of character.

So I sat in the congregation the day he delivered our family's truth and spoke to a church that serves 7,000 parishioners about

the good doctor and his extraordinary sacrifice from the Catholic perspective. My heart quite literally felt as if it might pound out of my chest as he recounted the litany of facts that led us to meet Dr. Andy in the first place.

Tears began streaming down my cheeks when he spoke of autism as a scourge and told the very real, unpopular truth about how incredibly difficult our lives have been since our precious Noah was diagnosed. In great detail, he explained Dr. Andy's unwavering commitment to our family and so many families who suffer as mine does.

Next, he addressed his unrivaled humility, genuine smile, and peaceful demeanor in the midst of a career destroyed, a country and reputation stolen not just from him, but his beloved family as well.

Personally, though, the moment I heard my father-in-law utter ‘MMR,’ all I could think about was what would inevitably happen to him. I mean, everyone knows vaccines cause

autism, at least everyone who has the sense to read the package inserts. But no one actually talks about it in public.

As the mother of a vaccine-injured child who repeatedly presents viable, repeatable science to doctors and researchers in the mainstream medical community, I am no stranger to condemnation, scorn, and ridicule. But my father-in-law worked 4 long years at his own expense to become a servant in this church community. This was his calling, and I believed by taking this risk, he was essentially ending his tenure as a deacon.

After mass, I practically ran to the back of the church, ready to defend him with my list of memorized studies, medical facts, and list of references, books, and conferences, and the names and numbers of families who successfully recovered their children from autism as the result of Dr. Andy's findings. But I was not needed.

When I finally reached the narthex, I

couldn't get near him. Lines of grandparents, mothers, fathers, brothers and sisters, godparents, aunts and uncles, nieces and nephews of those suffering with autism stood between me and my father-in-law.

I watched as emotional parishioners, one after the other, tearfully thanked him for having the courage to tell the truth. They shook his hand, grabbed his shoulder, looked into his eyes, and hugged him. They smiled and nodded one after the other, ‘Thank you. Thank you for telling the truth. Everyone knows vaccines cause autism.’

Now I'm telling you this today because I know who you work for. Megan is here to tell you who I work for. I work for my son, Noah Patrick Goes, who works harder than anyone I've ever known.

I work for my family and for the children of this country. I work for those who have been harmed by the food and drug industry and those who will be harmed by the food and drug industry because you refuse to

follow up on expert testimony of scientists and doctors like Dr. Arthur Krigsman and Dr. Richard Frye, who have the courage to speak up about the chronic autoinflammatory illness plaguing the most vulnerable consumers in this country, our precious children."

Dr. Insel: We're right at 5 minutes. So we'll need to have you wrap up pretty soon.

Ms. Davenhall: Okay. There's only a little bit more.

"Now you know the mothers and fathers of this country know what's happening to our children. You know we are intelligent and thoughtful. And now that we are 1 in 28, we are everywhere.

We are presenting the truth. Studies performed outside the legislatively protected labs of the pharmaceutical industry to the medical field. We are holding special meetings with our children's teachers, explaining to them why our children behave as they do and how it happened.

We are talking to other parents and

community servants. We are contacting our local and State representatives. While we do not have the power to write large checks, as your benefactors do, we are infinitely powerful in influencing the market by simply sharing the truth about our children with our fellow citizens, who, as I mentioned before, already know.

I encourage you to listen with open ears to the testimony that is now a matter for public record. I encourage you to read the package inserts on vaccines for yourself. I encourage you to revisit your job description. You are public servants.

Megan and all the educated parents here look forward to the positive changes you will be making and the great strides in autism treatment care that we can look forward to as you take this information back with those with actual power and thoughtful implementation for a meaningful standard of care for autism. Because at this juncture, autism affects more children than cancer,

diabetes, AIDS, and leukemia combined.

Yet in a country that prides itself on exceptional medical care, there is absolutely no standard of care for autism. No protocol to follow, no instruction for hospital employees to follow for the most common illness in our country. Autism is medical.

Now you are empowered to do something about it because knowledge is power. Every autism diagnosis from this day forward that is not thoroughly investigated from a medical perspective is your burden to bear. I, along with my legions of educated and thoughtful friends, will be watching.

Thank you, Lisa Joyce Goes.”

Dr. Insel: Thank you.

The next comment is from Carolyn Gammicchia. And again, we'll have to just abide by the 5-minute rule.

Ms. Carolyn Gammicchia: Today I'm here, and I understand why we're all here today for the Strategic Plan and going through Questions 1 through 3 minimally, and we're

going to go through the other questions. I want you to just all think about one basic thing, and it's the human rights of all individuals, human rights of individuals with disabilities, human rights of individuals with autism, and to collaborate together to ensure that choice options are offered.

When you construct and create the Strategic Plan, what I want you to do is to look at the things that I show you today and actually think about it in the back of your mind and why it's important that you think of the people that you're serving, individuals with autism, that they are not just a diagnosis, that they're individuals and people that are entitled to basic human rights and choice options, not only for those individuals but their families that are making those for medical choice.

And the main thing and the reason that I'm here today is our son, presented here July 9th. Our son was given a diagnosis of autism at age 2, and we were told that he

would have to be institutionalized before he was age 10. He now is in college, and he's made the dean's list twice.

And that would have never happened without biomedical interventions and without overall wellness and a doctor that would actually treat him for the health conditions that he was living with.

There was a time when I took him -- because he had nausea and headaches -- I took him for an upper GI that was prescribed by his medical doctor. They performed the procedure, and the doctor said to me, "Why are you here?" And I said, "Because my son is sick." He goes, "But your son has autism." And I said, "My son can still be medically ill as an individual with autism."

From that day on, I knew that I had to change this, and I knew I had to support the people that were working hard to ensure a basic human right. Because a person lives with a disability or a difference does not mean that they are not entitled to basic

human rights, and these are them. They are what I am entitled to as a person when I go to see a medical professional, and we all should be entitled to that.

So I'm asking -- I'm here today, traveled here from Michigan, to ask -- you to think about these things when you do your work as this Committee. I've heard some great things today, I really have.

And Dr. Insel, when you say in the last 5 years what advancements have been made? There have been some great acknowledgments by this Committee that we are looking at a medical condition beyond what's transpiring with genetics. I mean, even the talk today just about brains and looking at brains and how our medical condition affects what happens in our brain.

My brother, after he died a restraint and seclusion death in a State facility, we donated his brain to the autism tissue program, and his -- that tissue was viable for eight studies that have given research to

allow us to know what is transpiring in the brains of individuals with autism and epilepsy.

So I do also -- when somebody mentioned brain tissue research, that to us is important, and we're all registered for that program. You can take anything after I die, please. I don't know if my brain is going to be worth much, but please take it.

So that's the other reason -- and I'm sorry, I'm going the wrong way here. How can I get to the next one? And I know I'm going to be out of time. But sorry.

Like I said, just basic human rights of choice options for health care. What's happening now with a lot of individuals, I'm actually advocating in this area for a lot of families across the country -- their children are being refused basic medical care.

We've had a couple of children die due to this refusal of choice options in medical care. They're not getting second opinions. They're not even getting acknowledged that

their children are ill. I still have, to this day, parents being told, "Your child has autism," and they're not being medically treated.

Another thing that I wanted to bring up, and I think it's very important what I'm saying now and about basic human rights. We're still looking at the medical institutionalized model of what a disability may be. We're trying to fix somebody rather than treat a medical condition. We're trying to use psychiatric and pharmaceutical medication, which is like pouring a can of oil over an engine that just needs an oil change.

It's not reaching those neurons that may be damaged by environmental factors. So I want you to consider what's transpiring within medical institutionalization and what seems to be a trend, and they're going into the psychiatric medications for the treatment of autism.

Dr. Insel: So we're right at 5 minutes.

So we'll need to have you wrap up.

Ms. Gammicchia: And let me just go through this really quick. I want to also broach -- you have my presentation, and I wanted to mention about social institutionalization, segregation, and when you go into scientific research, I would also ask that you please look at applied research in the area for adults and teenagers in helping to support nonsegregated environments for living conditions and housing and work options.

And also look at the principles of self-determination and choice for individuals with autism as a basic human right. Once again, this I actually took from your Web site, and this is the task of what the IACC is. And I'm just going to remind you the last sentence one of the tasks are "to enhance services with the goal of profoundly improving the lives of people with ASD and their families."

Providing medical choice is one of the ways to do that, and this is your legacy.

You're all here for a reason. I know you want to do good. I'm a parent, but I'm here because my son is doing well, and I'm thankful every day for that.

But there's a lot of families that we support that don't have the same options. They're not being given the same choices. And this is your legacy. What happens here, I would not want you to live with something because of an option you didn't choose to make.

So I thank you all for your time today, and I appreciate you letting me present.

Dr. Insel: Thank you.

We're going to go on to Linda Varsou.

Ms. Linda Varsou: My comment is about the question, is IACC in denial of denial? Because in general, we are a society in denial of many things and issues. But in autism, the problems of chronic denial -- or in other terms, nonresolution, nonacceptance from at least one parent, usually the father, of their child's autism or of the degree of

the severity -- is as high as 50 percent.

You understand the devastating consequences in the family and especially in the child with autism, which is the final victim. Back in April this year when I first introduced this issue of denial, I had not data searching, but now there is a fantastic article, excellent study from Israel. This is good scientific research reporting denial as high as 53 to 57 percent of one parent to be in denial.

And this study has a bias also because of the participation of the families were voluntarily. That means the families were not so much in denial. So this is a main issue because regarding all the collaboration with professionals fails in some extent. All the scientific results that you have in studies are partial and they are biased, and what to do, of course?

It's very easy and with no extra money to every new research starting now or ongoing research or even past research to add the

factor of denial, and there are questionnaires and protocols to assess that very easy.

I heard before for the factor of prematurity or not, you said, but I think every study, every protocol -- the first thing they'll ask you is how was the labor, the delivery, and everything. So those are factors not to start a new study about prematurity, but to go back and find the results because they are there.

Okay. And let's see because we need to have this factor to find in the U.S. what is the percentage of the denial? Professionals tells us, estimate that around 45 percent. Do you understand the drama around that? So unless we can find within 1 year, I'm not saying more, the prevalence of denial in the United States, what's next?

How to cope with this serious problem? There are many ways. There are many ways, and also the questionnaires to the parents can bring, add some questions and can bring

solutions, ways to go. And at the end, we have the supreme level, the judiciary system, which can consider denial of a child's autism from a parent as a child abuse.

We have to take some measures to do something because all -- if autism was not existing, no one was here today. If denial was not existing, I was not here today to talk about that. And you have an excuse not to understand what is denial due to the fact that you are here; you are present. That means you are not in denial yourselves, okay?

And people that you know. And --

Dr. Insel: So we're nearly at 5 minutes. I'm going to need to have you wrap up pretty soon.

Ms. Varsou: Yeah, yeah. So I propose a low-cost, very fast study to find the prevalence and also have some solutions from families, and then because I reported in my documents a concept that I initiated about an autism-friendly society will benefit us all. It's very important because that could answer

different questions that I heard this morning here.

This concept started from the Autism Society of America when they had these autism-friendly movies. I don't know if you have been to those movies. They are movies with no dark room, low noise, and all the violent scenes from the movies have been eliminated. Don't you think that these types of movies are not the best movies for all children and all of us?

And going back to other issues, for my son, in the past -- now he's 28 -- and trying to see when he was in crisis, when he was doing very bad, I found out that when -- not all of their environment was -- like changes and things like this were disruption and not continued, then we had the crisis.

Finally, we -- finally, the autism-friendly society will be the best society for all of us, and I hope that the crisis, the economic crisis will bring us back to our roots, to our normal human physiology, to

human relationships, to what everyone needs, believe me.

This is my conclusion. Thank you.

Dr. Insel: Thank you.

We'll move to on Michelle Guppy. And again, we are so tight on time. I know we have your written comments that are much, much longer than 5 minutes. So I just hope you can revise and --

Ms. Michelle Guppy: No, I -- yes. I'm at 4:57.

Dr. Insel: Okay. Thank you.

[Laughter]

Ms. Guppy: My son Brandon is 19 years old. He was born perfectly healthy and is now severely affected by regressive autism from vaccine injury. He cannot read, write, or speak. He needs assistance with the most basic of life skills. He must have constant supervision because he has no sense of danger and will wander off, given the slightest of opportunities.

He has bowel disease, autoimmune

disorder, allergies, and the list goes on. He suffers from uncontrolled seizures that cause him great harm. I am unable to work outside the home because it takes all my time to research how to help him, advocate for him, and care for him.

At times, he endures such pain. The frustration of not being able to communicate what hurts causing him to bite his own hands to the point of bleeding.

My autism advocacy journey began right here in Washington, D.C., 13 years ago today at an autism rally and congressional hearings. In all those years, I have not seen any real strategy or actions to address the crisis that is the epidemic of autism. I have only seen the number of those affected increase.

Any help I have received has been from other parents or from doctors who themselves have a child with autism or, if not, who have actually listened to parents and dedicated their lives to truly helping them. I live 30

minutes from a major medical center, yet they have given me little to no usable help. When I meet with those doctors, it is I who educate them.

It was years before I found medical help 2 hours away for my son to be scoped in evaluation of and treatment for his GI issues. I believe my son would be dead had I not found a doctor 16 hours away who I now consult with for treatment of issues traditional doctors would never acknowledge.

There is something wrong with the system where insurance covers doctors who do not help, but not a dime for the ones who do. There is something wrong with a prescription drug program that covers pharma's drugs that do not help, but not those vitamins, supplements, and herbs prescribed by my doctor that very much have helped heal my son. There is something wrong with funding studies that produce the same conclusions, yet take no action to address them.

I can summarize them all with this. My

life with autism is harder than anyone could ever fathom. My marriage does suffer. My typical son does get ignored. I am stressed beyond oblivion. I am bone tired, and I am desperate for respite.

My son needs recreational programs appropriate for him. I want him to live in my home, be a part of my community. He needs services and supports that I cannot afford, given everything else, like a lifetime of care for him that I must somehow provide for.

There is something very wrong with funding study after useless study about what might cause autism except for the one study that can prove a major cause of autism, where we track which mothers go into vaccine clinics and which ones do not and whose children are healthier.

We need medical centers that partner with researchers and holistic practitioners for a whole-body approach to treating autism. Autism Is Medical did a survey where 89 percent replied that they sought health care

through alternative practitioners or managed their own child's health problems because they could not get adequate health care for their child in mainstream medicine.

Eighty-five percent replied that mainstream physicians are not familiar with the health problems their child has. Seventy-one percent feel their child's medical needs are ignored and told that their autism is psychological and, therefore, their symptoms do not need to be investigated. Eighty-seven percent feel their child has less access to appropriate health care across all settings than a child without an autism diagnosis.

Action must begin with those sobering percentages. To even begin to address the needs of the adult population is something that should have been started a decade ago. There is an entire generation like my son who will age out and have nowhere to go that their parents can afford for them to continue to learn, work, or further develop life skills.

I live in such fear each and every day. Fear of what new vaccine will be forced upon him. Fear that if I don't comply, I will lose the precious few services I do get or, worse yet, lose custody of my son and someone else determining that they know what is best for him better than me, his mother and my God-given mother's instinct. Fear of what happens to him once I die.

My presence here is very much me overturning the tables in the temple where the moneychangers of pharma, vaccine manufacturers, Monsanto, and GMOs have desecrated my child's health for nothing more than profit. To me, they are a den of robbers who must be held liable for the damages the toxins in their products have inflicted upon my son. The CDC and the NIH must be held accountable for their inaction.

I guess one thing has changed since the last time I was here. The status quo is no longer good enough. Parents like me are many, and we no longer believe the lies told to us

in what does and what does not cause autism. We know the truth, and we will continue to speak it. We will never quit.

Dr. Insel: Thank you, and I know some of you have come a long way to be with us, and we really appreciate this.

Moving on to Carol Fruscella.

Ms. Carol Fruscella: As a parent of two on the autism spectrum, I can certainly say autism affects every child differently. My one son is recovered and is now in college. One of my many fears is that that son someday might have to leave his chosen career path to care for his much more severe brother.

I placed my oldest son on the Ohio county waiver list for housing in July of 2004. At that time, it was a heartbreaking choice because he was only 12 years old. His number given to him that day placed him in line for services. That number was 198.

Today, at age 22, his waiver housing number, unless something very emergency based happens to me or to him, is 134. That means

64 placements have been made in a county 30 minutes from Cleveland, Ohio, and another 30 minutes from Akron, Ohio. On an average, that is 7 residential placements made a year for all different forms and differences and disabilities.

So using that average, it will be 19 more years before my son, who was 1 in 2,500 -- not 1 in 88, 1 in 2,500 -- will be up for his natural order in the line of housing choices, and that's as long as nobody in the 1 in 88 has a medical emergency or loses a family or jumps -- I'm sorry -- or jumps in place ahead of him.

I have a farm property in Pennsylvania left to me by my parents. I would like to build a residential center there for my son and others like him. There is just one problem with that. My son's Ohio waiver will not transfer to Pennsylvania. So if we were to move next week and somehow I'd be able to resource and build a facility to help individuals like my son and my friends'

families, my son would never be in that facility because he'd be moved to the bottom of the Pennsylvania waiver list.

My son has also had medical issues, and as he transitioned from pediatric into adult health care, I contacted no fewer than nine doctors, nine adult family practitioners that actually nicely said, "We prefer not to see your son," which is heartbreaking because an earache is still an earache and an ingrown toenail is still an ingrown toenail.

And I realized just sitting here this morning we've come so far, but there is still a whole generation. As you guys are kind of gearing up, we're talking about half a million people who are going to need housing in the next 10 years. And that's a lot, and we don't have the room for them now. If you don't have the room for the 1 in 2,500, I think there's a problem.

And to end, no one knows this more than our military families because as they move and serve our country and travel all over the

United States, their children go with them, and they go to the bottom of the services to every State they move to. I think we can do better, and I know we can. Thank you.

Dr. Insel: Thank you.

And finally, the last public comment on our list is from Dawn Loughborough.

Ms. Dawn Loughborough: Good morning. My name is Dawn Loughborough, and I am the single mother of three great children. Two were adversely affected by their vaccines. One has regressive autism.

I'm here today to give input to your health strategies for regressive autism. If we are truly to serve the child with regressive autism, we are going to have to rethink the face of autism from that of a psychiatric behavioral condition to that of a response to the environment condition. The challenge you will have with IACC, Dr. Insel, is making that shift from regarding the tire on the car and now looking at the glass on the road.

Regressive autism is most visible child impacted environmentally but by no means the only affected children in our society. We are seeing 54 percent of children in the United States with chronic illness, such as asthma, allergies, learning disorders, and other chronic illnesses, directly correlated with exposures to chemicals, pesticides, and toxins.

For example, one study recently showed an increase in midline birth defects, such as hypospadia, correlating with PCBs in those children's umbilical cords. The bottom line of what I have to say today is that environmental causation research, as it relates to health outcomes, is impeded by corporate messaging interests that will spin out counter research for every risk factor that independent researchers bring up in order not to change their practice to manage to the interest of our public health. We saw this with Agent Orange and our Vietnam veterans.

I've actually seen outrageous statements made on aluminum being an essential metal and good for pregnant mothers in vaccines on what you would think would be highly credible and reliable Web sites guiding prospective parents.

And we have to look at what is being injected into our babies, what is ingested by our babies, the contaminants in our water and the pollution in the air that we breathe, and we have to create an accountability for change that will impact the future well-being of children on the planet.

I want to bring to your attention just a few areas of studies that shine some light on this. First, let's talk about food.

Genetically engineered plants have been consumed by most Americans since the late 1990s. Industry-independent research is showing the detrimental effect that insecticides, neonicotinoids in genetically engineered crops with glyphosates, which is Roundup™, and vaccination can all cause

oxidative stress within the mitochondria, which seems to have a link to autism with more than one of these risk factors.

And we now see children getting food saturated with insecticides; GMO dairy, soy, and corn; and multiple vaccinations. At this same time, this generation of children are perhaps more vulnerable to and not excreting these toxins well.

Second, let's talk about metals. Aluminum is ubiquitous. It's all around us. It's a causative factor in neurological diseases and autoimmune responses, in particular for populations that may not excrete aluminum well. So it's not just being exposed to it. It's the ability to get rid of it.

Vaccination exposure now in utero is promoted by the CDC, with the CDC's internal knowledge that earlier exposure to mercury and thimerosal increases the risk of regressive autism. As the IACC, it would be imperative to recommend that pregnant mothers

not be given vaccines containing aluminum or mercury until the risk of regressive autism is ruled out.

Please reference the Price et al. study from 2010 that shows increased risk in regressive autism from thimerosal vaccine exposure in pregnant women. Also, please note that the IOM was told to exclude thimerosal from its scope in its 2007 vaccine safety study.

And last, please note that the lead investigator on over 20 vaccine safety studies at the CDC is under question, bringing all of the body of evidence safety studies into question for validity. In utero exposures will make it very difficult to study regression in autism.

Next I want to talk about the 2009 research from Japan that's showing that vaccination is leading to autoimmune dysfunction.

Dr. Insel: We're right at 5 minutes. So we'll need to have you wrap up.

Ms. Loughborough: The authors of the Kobe University Japanese study concluded, "Systemic autoimmunity appears to be the inevitable consequence of over-stimulating the host's immune system by repeated immunization with antigen to the levels that surpass system's self-organization criticality."

If we're going to get into resolving regressive autism and preventing the increase in prevalence, which I implore that you do, we have to move beyond dancing on the surface at the behavioral and social levels and go to the underlying medical underpinnings that result in regressive autism. Thank you.

Dr. Insel: Thank you. And again, I wanted to express on behalf of the IACC our gratitude for all of you for speaking up and speaking out and traveling sometimes great distances at great cost to you personally to share your experience with us.

This is not a typical IACC meeting, so we won't have a period of further discussion

about the comments. We'll have a chance to come back to them when we do meet in our regular meeting in the future.

But because it's a workshop and we have a huge amount of work to get done before the end of the day, I'm going to suggest we stop at this point. We can grab lunches, but we're just not going to have time for a leisurely lunch.

If you can grab food and get back in the next few minutes, we want to start working while you eat so we can make sure we don't run out of time on Questions 4, 5, 6, and 7.

Susan has a comment as well.

Dr. Susan Daniels: So we had the invited participants and the IACC members order some lunches ahead of time, and those lunches should be delivered here. And so we can have you all pick up your lunches and then come back to the table. And in 15 minutes, we're going to start the meeting back up, and so we planned for a working lunch.

For those who do not have a lunch, one

of the downsides of this lovely room and building is that there isn't a cafeteria in this building anymore. The cafeteria closed.

And so there is a cafeteria across the street at Building 31. If you go out the front door of Building 1 and turn left, cross the parking lot and the street to Building 31, and the cafeteria is on the first floor. And then you would have to return to this building.

And if you have not paid for your lunch yet, your boxed lunch, please go to the registration desk to pay. Thank you.

(Break)

Dr. Insel: We're going to try to get back on schedule and work while we eat. There are a few people -- I've been delaying because there are some people who had to go over to Building 31. Hopefully, they will be back.

We're going to invite those on the phone back as well. And I'm going to start with Question 4. You know, it's so interesting,

this whole process that we go through because on the one hand, we try to get deep into the scientific opportunities, and we talk about all the great progress. But then at the same time, we hear public comment about still just the extraordinary state of what life is like for families.

And it's just so obvious that we have a very long way to go. And some of those issues are scientific, but some, as you heard in terms of the housing waiver in Ohio, are going to require us to in another format do a deeper dive on where we are with the services for families. And certainly, this consideration that comes back over and over again about lifelong needs will need some further discussion.

That's really not the topic for today, since we have a very focused agenda of trying to define what we know and what is new over the last 5 years. There are some new members that have joined us or new experts that have joined us since we started this morning.

And I want to make sure we capture everybody who's with us, I think, and I'll try to do this when you're not in the middle of a bite of food. Scott, could you just introduce yourself and let people know?

Mr. Scott Badesch: I'm Scott Badesch, the president of the Autism Society of America.

Dr. Insel: Welcome, and you were part of Questions 5 and 6. Is that right?

Mr. Badesch: Yes.

Dr. Insel: Okay. And John O'Brien, you're from the IACC, just --

Mr. John O'Brien: John O'Brien from the Centers for Medicare & Medicaid Services.

Dr. Insel: So John, I don't know if you have a seat at the table, but I can guarantee that when we get to Questions 5 and 6, you'll be at the table in one way or another. There will be lots of questions.

Is there anybody else who didn't have a chance to introduce themselves earlier? Yes, Laura?

Ms. Laura Kavanagh: Good afternoon. I'm Laura Kavanagh, and I'm with the Maternal and Child Health Bureau at the Health Resources and Services Administration.

Dr. Insel: Dan?

Mr. Dan Hall: My name is Dan Hall. I'm a parent of a 17-year-old on the spectrum, and I'm the manager of the National Database for Autism Research.

Dr. Insel: Dani?

Dr. Fallin: I'm Dani Fallin. I'm the chair of the Department of Mental Health at Johns Hopkins and the director of the Wendy Klag Center for Autism and Developmental Disabilities.

Dr. Insel: Dr. Dawson? Sorry.

Dr. Dawson: And I think Jim Perrin, too, came in late, right?

Dr. Insel: Okay.

Dr. Dawson: So, hi. I'm Geri Dawson. I'm on the faculty of the Department of Psychiatry at Duke University and director of the Duke Center for Autism Treatment and

Diagnosis.

Dr. Insel: I noticed your nameplate changed over the course of the morning. So either you got a new job since 9:00 a.m., or we just are catching up with your transition. Welcome.

And Jim?

Dr. Perrin: I'm Jim Perrin, and I'm a pediatrician at the Mass General Hospital for Children. I'm president-elect of the American Academy of Pediatrics and have been until recently heading the Autism Treatment Network and Autism Intervention Research Network on Physical Health.

Dr. Insel: Is there anybody on the phone who's joined us since this morning?

(No response)

Dr. Insel: Is there anybody on the phone?

[Laughter]

Unidentified Male Speaker: We listen with bated breath to your every word, Tom.

[Laughter]

Dr. Insel: Well, that said, we'll start on Question 4, "Which treatments and interventions will help?" Here our aspirational goal is, "Interventions will be developed that are effective for reducing both core and associated symptoms, for building adaptive skills, and for maximizing quality of life and health for people with ASD."

So I was just asking Susan who is responsible for this, and she pointed to me. So let me take you through. We had a couple of very good discussions and then an additional call, which I missed, actually, which happened just yesterday. So I may need help from some who were on that call.

But much of what we heard about, what you'll see in the portfolio analysis, is that there are some areas where we've made investments, others where we're still sort of shy of what the original goal would be. I think people have the sense that this is an area where, ironically, we're spending a lot

of money on too many studies and maybe not enough in any definitive way to come to anything conclusive.

I usually note that most Phase 3 FDA-required studies or FDA-aligned studies would be somewhere between $50 million and $100 million to complete, and we, I think, in this portfolio had something like 280 studies for like $20 million or something like that. It's so far off from -- it's an order of magnitude off from what one would expect.

Altogether, there was $309 million invested for Question 4 around treatments and interventions. You can see up on the board we've listed a number of what people thought would be required going forward.

There is, I think most of all, a sense of real promise from some of the work that's been done both on the behavioral side and on the biomedical side, but real concern that we still don't have the optimal outcome measures and that we have to put some work here into getting the process of doing clinical trials

in this area up to speed so that they can be done faster, cheaper, better -- with outcome measures that might use biomarkers or some surrogate marker rather than waiting 6 months or 12 months to look at behavioral change. It's very much in line with what we heard earlier today about screening and diagnosis.

Continuing concern about underserved populations and absence of studies that really look at diverse populations and then again a theme that started to emerge a little bit in our earlier conversations -- I think it was Julie who said they need to focus on individuals and not just groups. Several people have made that observation.

Here, too, a real concern that the studies that have been done are with autism broadly written or broadly defined, sort of like a *DSM* sort of classification. I think most people would agree that doing an intervention on *DSM* autism would be like giving antibiotics to everybody with fever. You're talking about many, many different

disorders that are under this very heterogeneous classification.

And if we're going to see improvements, we're probably going to have to break out the subtypes and begin to find ways to provide different people with different kinds of interventions. That was one of the themes that came out of the conversations.

Let me now ask for those who were on the phone call from yesterday, and since I wasn't there, I can't even tell you all the members of that phone call. But hopefully, somebody from that call would be able to weigh in.

I know, Jeremy, you were part of that discussion? Maybe you can do a better job in sort of summarizing where we're at, and the question on the table again is compared to where we were 5 years ago, where are we in 2013?

Dr. Veenstra-Vanderweele: So we were actually quite enthused to be able to say that there was much more data out there now for behavioral intervention certainly than

what you would have seen 4 or 5 years ago. Early Start Denver Model would be sort of the shining star in that area.

But concerned that there and sort of everywhere, there tends to be not as much power as you'd like to see, that we tend not to go to scale, that we don't necessarily have a sense of who benefits in a measurable way at the front end. And then we also don't have a sense from an effectiveness standpoint what happens when you take these things out of the academic setting and into the community and try to scale them in a financially feasible way.

This is -- you know, that, as a great example -- is a treatment that very, very, very few people in the country can actually access. And ways to study it in such a way that we can look at expanding access is important.

On the biomedical side, we've made a lot of progress on the preclinical side. There's more progress yet to be made. We need to

continue expanding the pipeline, and that's, I think, where we will continue to see progress. We've actually seen trials of medicines for core symptoms, which is remarkable. But where we're struggling is to figure out when we think we see a signal, who are we seeing it in, and how do we measure what we're seeing?

And I think that that's a substantial challenge, and we talked about a number of ways to tackle that challenge. So one way is to think about the narrower groups where you are more confident you're going to see a signal because you have a clear understanding of neurobiology, like in fragile X syndrome, tuberous sclerosis, and so forth.

And another thing is that we need to take those things that we really think work and use them as our testing ground for outcome measures so that we actually can evaluate what outcomes are most -- outcome measures are most -- sensitive to change in a place where we actually are likely to see

change. Because we can implement these all over the place.

Some studies are going to fail because the medicine doesn't work. Some studies are going to fail because we don't have the right way to detect the improvement that happens with the behavioral treatment over a short period of time. And there are so many unknowns there that we need to start with what we know and build outward.

So those are some of the things that we talked about. There's a lot left to do here, but there are actually some leads that will lead to, we hope, rational clinical trials on the medicine side, and there are ways to grow what we know on the behavioral side outward and make a big impact for more families.

Dr. Insel: Paul? Additional comments?

Dr. Wang: Yeah, I was also on the call -- as was Idil, who has her hand raised -- 2 days ago.

I think Jeremy has hit on the major points that we discussed. Just to flesh out

one in particular, we noted the fact that many will be well aware of that there are many drugs that are on the market, available, approved for use in conditions that are related to autism, at least as secondary or co-occurring kinds of symptoms, for example, for attention deficit, for sleep, for anxiety.

But their use, their safety and effectiveness in the ASD population is poorly understood. There have begun to be studies of those drugs, but as Jeremy said, a lot more work remains to be done there.

I'd also second the comment that you made, Tom, in the introductory remarks on this question: the need for an understanding of the dynamism of various biomarkers.

We have done much research now on diagnostic biomarkers for autism, but in very few cases do we understand which of those biomarkers do show change, either just longitudinally with maturation or specifically in association with symptom

improvement, and we need to have much better understanding of that to support intervention trials.

Dr. Insel: Idil?

Ms. Abdull: I also agree with Paul and Jeremy, and we also talked about yesterday, or the day before when we talked, which interventions or treatments should I get for children with ASD but who also have other disorders, such as sensory processing disorder. And a lot of times, insurance companies don't cover that because we don't have enough research to say this is a symptom of ASD.

And we also in terms of underserved populations -- that would probably be more about Question 5 and 6 -- but a lot of these children are not getting the services because of the kind of coverage they have, which is Medicaid, which doesn't always pay as well as private insurance or doesn't cover.

And then we also talked about the Early Denver Model -- that's obviously a good one -

- and the early intrinsic therapies, but those are for younger children. So when a child is diagnosed later, like 5 or 6 or 7, as many minority kids are, then there aren't really interventions or treatments that you can get, other than just the special education.

And so I think that that's a gap that we need to figure out a way to address those things and figure out a way to help children who are diagnosed at a later age. And so those were some of the things that we also talked about.

Dr. Insel: Great points. Other things? Jeremy?

Dr. Veenstra-Vanderweele: So reflecting on that, thank you for reminding us of some of the things that we talked about. It's hard to keep all of this in your head at once. But there are some areas where we've really extended our knowledge, like in ADHD treatment in the context of autism, but there are other areas where they really haven't

been as emphasized -- so anxiety treatment in the context of autism.

Both of these things happen in the majority of kids with autism, if you measure them the way we know how to measure them, and yet there's a clear slant to funding treatments for hyperactivity and not so much treatments for anxiety. And I think that there are places where you see those imbalances in the portfolio that are built around opportunities, right? So if you have things that you can adapt, that's an opportunity.

But I think here is one where we really haven't taken advantage of an opportunity, and I think sensory integration therapy is such a common thing that's used. There is not nearly enough data on it, which is why it's very difficult to get that funded. And there are a number of examples of things like that that just haven't taken hold from a data perspective despite them being used very frequently, and we need to sort of leverage

resources there, too.

Dr. Insel: In one of the discussions we had, I guess it was the first phone call, really struggling with what's the right balance between investing in studies to show that currently used treatments are not worth doing versus investing in studies that might actually give you something that we think has real promise. And there seems to be a need for both, and I think, as a group, we weren't really comfortable knowing exactly where to draw that line.

Brian?

Dr. Boyd: Yeah, I want to just expand on a couple of points that were made earlier, but also bring up some new things. While I do think it's really important, to just mention again Geri's study is showing that behavioral intervention can have an impact on brain development. I think we thought that but didn't know it before this study showed that.

And the other, as Alison said, is that we did really think there was this critical

period for language development and autism. And that if it didn't come online by 5 years of age, kids wouldn't develop functional speech. And because of Connie's work and Ann Kaiser's work and others, we are learning that you can use targeted behavioral interventions applied later and still see gains in kids' language skills.

I think the other thing is we are really beginning to do more comparative efficacy work. I was involved in some of that work where we're beginning to compare treatments that are out there because there are a number of treatments that already exist, and we need to know if those ones work for kids.

The other thing we are learning is that we thought at some point that combining different treatments wasn't a very good approach, but this is what community-based providers are doing. They've been trained on lots of different things, and they're taking from different places. And they're trying to figure out how to put it together to best

serve the children they're working with.

And what we're sort of learning is that this eclectic approach, this idea that these providers may be jacks of all trade but masters of none may not be a terrible thing. That it can lead to possibly good outcomes if they are combined in certain ways.

So this knowledge of eclecticism is one we need to study. How are providers making decisions about how they combine things, and are they leading to as good of outcomes as some of the specialized interventions that we're now developing for young children with autism?

And I would say on the underserved population end, I think we're learning more about how to recruit groups, individuals from underserved populations, and some of the more courageous strategies has been we need to retain the sample. I think Amy has been involved in some of this work as well, but I don't know if we know a lot about outcomes related to that.

So we are just beginning, just in the beginning stages of working with families of underserved populations.

Dr. Insel: Yeah, I just want to add on to this because I think it's such a critical point, and as we think about what the language in our report says, and this isn't just related to autism but across the board what we think about a lot more at the NIH is that we're already providing treatments for 300 million people in this country. We just don't collect the information. We don't treat it like an experiment.

And a classic example of this that came out to us was there are over 100,000 people in the United States who are getting deep brain stimulation or at least globally getting deep brain stimulation for Parkinson's disease. And no one has ever bothered to sort of build a scientific payload on that project to figure out what it is -- you know, who is responding, who isn't, what is the response rate? All of that

information.

It's being done as a kind of clinical intervention without ever getting the feedback loop. And we ought to really be thinking about this. The ATN, which is something that came up a little bit today already from Jim, is sort of one opportunity we could point to in terms of progress, that that's been established with HRSA and Autism Speaks involvement as an infrastructure to create some of this.

And so we didn't have that 10 years ago or even 5 years ago, I guess. So there are now 17 centers, and that was one of the, you know, in terms of describing for Question 4 what's been accomplished, in addition to saying specifically we did these studies and got this information, a lot of it really is going to be still building that infrastructure. So having a large-scale network like this, having -- for the first time -- having industry engaged.

So we have -- we've seen the first

serious movement by big pharma to say, gee, autism is maybe a market, and maybe we need to start investing there as well. That was not true 5 years ago. It's certainly true today in a few companies. So that's, I think, a really positive sign.

There was a hand up over here. Yeah, Aubyn?

Dr. Stahmer: I just wanted to reiterate what Brian was saying about our need to look at what's happening in community settings. I think that's some progress we've made in the last 5 years. Five years ago, I think we had no idea what anyone was doing in the community setting, and now we at least have a cursory idea.

And that on the issue of subtypes, I think that it's going to take us a while to figure that out, especially behaviorally. Community providers are figuring that out every minute of their day because they don't really have a choice. It's difficult for them to articulate it, but I think by going in and

working closely with them, it might help us understand how to choose which intervention when and get some data to support it, rather than just that clinical judgment word.

So I had one other thing, but now it's gone, so that's all.

Dr. Insel: Good. All right. Alison?

Ms. Singer: I think one area where there's still a lot of work to do in this section is standardizing the outcome measures and determining more objective ways to measure the results of clinical trials. I think, for example, so many of them are based on parent reporting, and one person -- one parent's 5 is another parent's 10.

So I think we've talked a lot about that over the last couple of years, but not a lot of progress has really been made in terms of that kind of standardization. Because I think we may be missing a lot of -- a lot of -- progress just because we're not properly measuring.

Dr. Insel: Right. And I think if you

talk to people who've been doing the clinical trials, that's the first thing they'll list as a challenge. There is a really urgent need for that.

Amy?

Dr. Wetherby: So when you look back at the past 5 years and you talk about randomized clinical trials, it's hard to see all the progress that's going on because it takes a long time to complete clinical trials. I've been involved in at least three major clinical trials, none of which yet have but very soon will, hopefully, have published findings.

We just finished the first one, which you helped me meet with Ann Wagner I think it was 7 years ago and begin to plan it. We've just finished that trial and are writing it up. We presented the findings, and we had findings. So it's exciting, but you don't yet have the findings.

But you've talked about, you know, the genetic research going on, and it's happening

right now. So I think it's important for everyone to be aware that there are a lot of findings coming out. I'm also part of the ARB, which focused on underserved populations. We just submitted a manuscript under review. So these randomized clinical trials are -- we're coming out with findings, but you haven't yet read about them, and I think some exciting new information is going to be coming out maybe before December.

Dr. Insel: So it's a good point. You know, the long lag between when we start and when we finish the trial and then another lag for analysis and another lag for publication. There is a report out just this morning online from Michael Lauer looking at the Heart Institute's here, their clinical trials portfolio. And pointing out that it's just way, way, way too slow.

And it would be unacceptable in industry to do a 5-year trial. They wouldn't do it, and FDA won't accept it often. So I think for academic trials, which is where all of this

has been, we probably are going to need to rethink how we do them, how we recruit, what the milestones would be like, what kinds of -- what kind of timeframe would we accept. Because, as you heard earlier, most parents aren't really wanting to wait 7 years to get results.

Dr. Wetherby: Well, if I could do a quick just followup? I mean, our trial, which took 7 years, we have 82 families. So it was almost twice as big as the Early Denver Start, you know, it was multisite.

We are now -- we're doing a study in the schools. And so, that's another, when you're dealing with older students, you know, the schools is a lab, and we're much quicker going to have a much -- we're going to end up with about 350 students over 4 years. So I think the school-age population offers us an incredible laboratory in the community, so doing community-based research.

Dr. Insel: Yeah. Good point. And so I just want to put a plug in here because I do

think that the culture of performing clinical trials is changing drastically. And again, another *New England Journal* paper just from last 2 weeks ago of one of the largest cardiovascular intervention trials done recently with spectacularly important results -- 7,000 subjects, total cost $300,000, $50 per subject, total duration 18 months. Done with a registry in Sweden.

There are ways to do this that we haven't been thinking about, and we need to get smart if we're going to be able to turn things around faster, better, cheaper than we've been doing. I can just tell you I was at the FasterCures meeting last week in New York City, and it's not just autism.

Across the board, families are saying whatever it is you're doing is too slow, too expensive. It's just not meeting our needs, and we need to look at that in terms of how we do this going forward.

Geri, you had your hand up?

Dr. Dawson: So I think one of the areas

looking forward is the need to understand those children who don't respond as dramatically to some of the earlier -- the early behavior interventions -- and to really be able to think about how we could promote or enhance neuroplasticity by providing either customized kind of add-ons.

You know, some of these could be different behavioral strategies. Some of them could be technological strategies, particularly if the child is nonverbal. Or they could be pharmacological add-ons and augmentations, or they could even be brain stimulation, such as in the case of transcranial direct current stimulation, which is a safe form of brain stimulation.

But the whole idea here is to really start thinking about the kids that haven't responded so we're not really using a one size fits all, but we're customizing the early interventions to address this major heterogeneity.

So the other issue I wanted to bring up

is that I really don't think we have tested the limits of understanding neuroplasticity throughout the lifespan. And I think that if we provide some interventions later in life that we're going to have some happy surprises about the kinds of plasticity that we'll see in adults.

I mean, just one quick study that we did in our lab. It's been published for a while where we were able to show that you could train adults with autism to become face experts, and you could see changes in their ERPs to faces. Not only did they develop good face recognition capability, but their ERPs to faces normalized.

So I really think that we need to expand this notion of neuroplasticity and take a lifespan approach and think about it from both a behavioral and a pharmacological perspective.

Dr. Insel: Thank you.

Carlos? We'll go around the room because there are lots of hands up, and then we'll go

to the phone.

Dr. Pardo: Geri's point is quite interesting on neuroplasticity, and I would like to emphasize in the need of earlier biological outcome measures and when we embarked on the minocycline study, one of the concerns that we had is how minocycline is affecting biological pathways. And we took the option of taking blood as well as spinal fluid and looking at growth factors, looking other potential pathways that give us clue of potential mechanisms and so on, and how does medication are affecting the mechanism?

And I think that brain plasticity is something that we need to tackle in the future because there is a lot of room between location and medications to modify brain plasticity. I mean, if we are able to identify at the same time mechanisms and the potential role of all of these factors in modifying those mechanisms, I think that there is going to be a value for that.

Dr. Insel: So I'm hearing from both of

you the need to maybe combine treatments as well and not look for some magic bullet that's going to be the --

Dr. Dawson: Right. Exactly. And customize.

Dr. Insel: Customize and combine. Other hands up here? Scott?

Dr. Robertson: So one area that was mentioned in here, and was mentioned I think by Geri in passing, was technology that can support folks -- adolescents, kids, and then, you know, as they age into adult life. And it's been a little bit disappointing on my end in terms of the -- that we've advanced a lot technology wise and in smartphones, iPads, and et cetera, et cetera. But I feel like our research hasn't often been coupled with that, with supports.

That we lack technology that could be helping, for instance, really well with, like, executive functioning, with sensory. It seems always -- seems to be focused only on social communication. I mean, we need to do

better in that area, too. But there are other elements, you know, in terms of the challenges that autistic individuals experience in early childhood and adolescence and adult life that we need to be doing better with technology.

And it's -- I don't know, maybe it's partly because of my background in comp sci initially and information science technology that I don't see that connection as well in health and wellness, and I feel like we're missing out on a lot, what one could be doing with both funding directly in HHS and coupling, kind of cross-braiding what's happening in the National Science Foundation and maybe kind of having cross-corroboration on research that can be helping individuals from the innovation -- the technology and the innovation -- on the health and wellness end.

Dr. Insel: Just to clarify on this, have there been well-designed studies of any of the currently marketed technologies? Because there's a lot of stuff that -- a lot of

companies are developing tools for people with autism. But has anybody actually studied those in a rigorous way?

Geri?

Dr. Dawson: Well, the one that comes to mind is Connie Kasari's study that Autism Speaks funded and then I think went on to help her compete for another NIH funding through the ACE Network, where children who had not responded to or had not acquired speech in response to early intervention were provided with a speech-generating device and to look at that facilitative effect in speech acquisition.

And so that's one example. But I would say, and I know Autism Speaks has really been focusing on this issue, which is that we're seeing an explosion of technologies and apps that are out there without really good empirical studies that support their efficacy or usefulness.

Dr. Insel: Our transcriber is worried. The sounds aren't coming through? Is that --

Court Reporter: They are now.

Dr. Insel: Oh, okay. That was Dr. Dawson. Or you could actually attribute that to -- who should we?

[Laughter]

Dr. Robertson: My background is that it kind of dovetails with what you were saying earlier, Tom, on how we have -- it was that group of 100,000 people in Parkinson's -- kind of a similarity here. The same on technology is that you have this growth on the uses of different apps that can be supporting things like the executive functioning, et cetera, happening out there in the world, but no one is studying that empirically. No one is studying different apps like Proloquo2go extensively in good field studies that are used augmenting communication wise.

So maybe we need to find a cost-effective way to be looking at that out in the field because we can't study it all, I guess, in the lab --

Dr. Insel: It's just such a great idea. It's amazing that it hasn't been done yet. But maybe somebody around the table or somebody listening in has already started.

There is certainly -- we saw yesterday, actually -- Paul was visiting with Google Glass and the opportunity to use what they're calling now social prosthetics, really interesting new technologies that can change a lot of things here beyond the classic development of medications or small molecules.

There were other hands up. So Anshu?

Dr. Batra: Thanks, Tom.

So I wasn't part of the second phone call. I was part of the first one with you, Tom, and I couldn't reschedule my patient load to be part of the second phone call, which brings me to the community practitioner, which is the perspective I would like to share.

I'm hearing the -- you know, the agreement -- from everyone here that we need

to bring the research into the community because that is what we're doing. That's what parents want. That's what we are doing, and we're seeing -- we are seeing -- remarkable improvements in our patients, in our kids.

However, I'm glad Dr. Perrin is here. I'm putting my medical license, my pediatric medical license on the line every time I'm doing something that doesn't have evidence-based practices behind it or I'm doing something, using something, off label, but it's showing benefit. And so as we move forward, we need to bring the research into the community, do what the community practitioners are actually doing more than what is happening in the academic setting.

And I think the issue around the process of the research, the peer-review research, the academic research -- we can't apply those same rules to the community-based sort of process. It takes too much time, as you alluded to. You know, 5 years is just -- that's a lifetime for a lot of people, and so

it has to be in some way abbreviated, shortened, customized for the patient population.

The issue around the heterogeneity, that is so critical. We all have heard one child with autism is one child with autism. They're snowflakes and their presentations are so varied, though they carry the same diagnosis. And I think we really need to be aware of that and understand the different phenotypes of the presentation so that that will help us customize the therapies to gain optimal success in helping in our patients.

The issue around the sensory-based intervention. Everyone is doing it. I can't think of one patient I have not recommended sensory integration-based treatment. And it is -- it is something that is so under reimbursed, underpaid for, but it is probably the most used.

And so we have to look at some of the protocols, some of the interventions we are using that -- not only sensory, but sensory

motor -- the things that I guess fall into the OT/PT realm, but it's not really compartmentalized. It's something that we're all using to help with certain aspects of that individual.

So I think we really have to make a shift from behavior and medications to more of, you know, the sensory motor-based interventions. And just simple interventions that we're all doing, that, you know, it's simple but we don't have any evidence to support it. And so we need to go and look at those, at the basics.

And you know, I think that was -- and the RCTs, they just take too long. I'm sorry. You know, my patients won't wait. You know, my son is 16, and 10 years went by, and I have very little to show for it except that -- except that -- you know what, he's doing great because of the out-of-the-box thinking that I and the practitioners in my community are providing for him.

The last thing I wanted to share was

something that Scott had mentioned, which is that we have -- there is a paucity of interventions that are looking at the cognitive phenotypes in these individuals. Once you get past the ASD diagnosis, these kids can learn, and they're very, very capable of moving forward in academics and in other learning processes.

And we are using certain techniques and programs that we're using -- and that we use for other diagnoses -- for children with learning disabilities and the hearing impaired, et cetera, et cetera, that we have to look at those programs within our population and see how they benefit the executive functioning, the learning capacities, the working memories, the variety of indices that we're -- that can -- that can help promote the function of our patients.

Dr. Insel: Okay. Thank you.

Lyn and then Scott.

Ms. Redwood: This follows along precisely with what you are saying, and I

just wanted to put in a plug because we think generally about treatments as being drug treatments or behavioral treatments. And there are a lot of things that parents are doing, the complementary and alternative treatments, that we really need to be providing some guidance on.

Nutritional interventions. There's been some exciting research out, using methylcobalamin and folinic acid, which in the past was proven to correct some of the metabolic abnormalities with glutathione metabolism. That just came out showing that it also resulted in significant improvement in their daily living skills, expressive communication, social skills.

So those types of things I think we need to follow up on rapidly and subject to, you know, further clinical trials. Parents are already doing these things. There are also things for the children that have mitochondrial disorders, like L-carnitine and CoQ10. Also NAC was recently found to be

effective for helping with some of the aggressive autistic behaviors.

So those are the types of things that I think we need to also be embracing because they can be equally as important as the drug therapies. So I just wanted to put in a plug for that, too. And they are also something that we could move on much more quickly.

Dr. Insel: I think -- Scott?

Mr. Badesch: Yeah, I hope what I say doesn't offend anyone because I really feel what everyone is doing here and saying is right on line. But I think there's a missing point, and that's the bridge of what you're doing to the general population that needs your help. And it's not coming through.

I mean, it may come through in a doctor's office, but in the community at large, a parent and an individual doesn't understand this. I'm sitting here -- I don't understand half the words you guys are talking about. And I think the ability to translate it into a language where it's

understandable.

And the second thing I see, and I know when we look at our parents and individuals we help, they're asking what does this lead to? I mean, we have to start taking that there are baby steps that are going to lead to an end product so that the end always isn't this one type of treatment or one type of service.

And then the other thing is, as we all know, you know, we go to the Internet, and there are 20 billion ways we could help our kids and 19 billion and whatever are horrendous. So how do we -- how do we -- present from the trials the benefit of all this to really helping people?

And the other question I would suggest when I went through all this was -- while I think it's great we're serving the underserved community -- there are no services in the underserved community. So to know what their issues are is wonderful. But until we commit to put services there and to

put the doctors and the social service agencies and the hospital care, we're failing to help those individuals.

So I think groups like mine and others have that responsibility, and we're falling short on it. I'll be the first to say that. But what concerns me is we're doing all this great research, but it's not getting through to the majority of parents.

Dr. Insel: That's very helpful. Matt?

Dr. Pierce: Hi. Just kind of following up on the repeated comments about the heterogeneity and how to tailor treatments to the right subgroup of kids. It looks like there's a movement, and I want to state that this is a really important movement, to try to get biomarkers prior to treatment.

So try to get signatures of different subgroups of kids before they're going into treatment. Because I think if you just look at IQ or language or various other things in an 18-month-old, that's not necessarily going to predict or tell you what type of kid

they're going to be in a few years, and it might not guide you what kind of treatment is the best.

But if we look inside the brain, there is starting to be some emerging evidence that you can get functional brain scans or ERP maps that might actually be a more direct roadmap to which kids are going to do better and which kids aren't, and that's going to help us give them the best treatments.

I mean, you know, Debbie Fein's work shows that 20 to 30 percent of kids recover and do great. Well, what do they look like biologically? And if we knew that when they were 18 months, probably get them recovered by the time they're 3 -- super fast. So just want to get a lot of biological measures before treatment. I think that's going to be very helpful.

Dr. Carey: I wanted to point out just one specific gap area I see. We had speakers come in earlier this year and talk about minimally verbal school-age children. And the

same team called up here, I mean, just published a paper, which I totally agree with the title, "Minimally Verbal School-Aged Children with Autism Spectrum Disorder: The Neglected End of the Spectrum."

We're not really looking at them. It was really driven home to me this last year in my own school district. I live in one of the largest school districts in the State of California, and they revamped their whole program in this past 10 years on autism to really focus and in doing so completely left out this population.

You know, in talking to them, when being shown a program completely inappropriate for my son, I was told, "Well, we place children in this program for a year, and those who just can't learn, we refer to the county program." Now when I recovered from just the shock of that statement, I realized the person who said that would probably really love to reword that herself.

You know, I realize that we're not

giving the schools the tools they need. We've neglected this area. We don't give them the tools they need to teach this population, and we don't give them the tools they need to measure advances in this population, right?

You take a 5-year-old who's minimally verbal and you give him 10 words, you've changed that kid's life. You give a typical kid who is 5 years old 10 words, and it's in the noise, all right? I mean, but if we measure based on number of words, right, if we measure based on the typical kid, we completely wash out that advantage.

And that actually happened -- I have to say we were part of a clinical trial, and you couldn't see the advances my son made during that clinical trial. You know, it turned out he was on the placebo arm of the trial, but at the same time he made a lot of advances. It just didn't come out because, you know, what we saw as huge advances don't measure when you measure by a yardstick.

I think it's basically exactly what Geri

was saying. When you use the same yardstick for all populations in here, you don't -- you miss the advances in that. And like I said, some of these can be just life changing. But if you just say, you know, if you measure based on the typical kid, you miss that.

So anyway, the big one is I think I would really like to see more. We brought them in, and I think we have a hole in that area. And I think we need to move on.

Dr. Insel: So we talked about this as a Committee and did some digging into it. I think there were 16 studies. It's one of the objectives. That's -- either it's 11 or 16 -- somewhere in there is the number of studies being done at about $9.5 million.

I think this is the issue that Amy brought up that, you know, for this question, even more than for any of the others, it's a long-term project. And if we did -- those studies were funded in 2011, which means they are still probably recruiting, and it's probably going to be another 2 years before

we have anything to look at from them. But it's in process.

So I think -- because we were concerned about that, too, on the call, and there was some discussion. It's 4 -- I don't know. It's like half way down through the list of 4.S.G. -- now whatever "S.G" means. And this was something that we had a question about -- really what do we have to tell people at this point?

And I'm afraid the answer is wait and see. It's not -- we just don't have the data yet, but it's underway.

Jim?

Dr. Perrin: So I have three I think unrelated comments. One is just to reassure Anshu that, unfortunately, I wish we did have evidence to support all of our off-label use of medications, but we don't. And your license really isn't at risk. So you're okay.

[Laughter]

Dr. Batra: You have that on record now, right.

Dr. Perrin: I'll go on record for that.

Second -- actually, I don't know all you've done. That's right.

[Laughter]

Dr. Perrin: I've got to be careful what I say there. Second, just to go back to the issue of pipeline and publication, and we've spent a lot of time building a clinical and research network through the ASATN and the ARP, and we now have about 45 publications from that. But I would say that half of that has been in the last 18 months over 5 or 6 years of funding from a variety of good people.

So it does take time. But having a network, we've now involved over 1,500 children in research projects through the Network, and that's a valuable resource for the future certainly. But it really does pay off ultimately.

And my third comment really gets back to Alison's and other people's comments about the need for outcome, and just to comment

that with CMS and AHRQ funding through the CHIP program, the Child Health Insurance Program, there are 7 Centers of Excellence in 10 state projects that are working on development of pediatric outcome measures across a spectrum of areas.

I have always been concerned that there's relatively little attention to chronic disease of any kind in the work of those seven centers, and you know, frankly, that's a resource that could be very valuable in the development of outcome measures today. It's funded. It's there, and I would encourage all of us putting pressure on those groups to come up with better measures of kids' and adolescents' functioning and use those much more actively in these kinds of trials.

Dr. Insel: Two last comments. Geri, and then Idil, you'll leave the last word.

Dr. Dawson: So this issue of a sensitive assay or outcome measure for clinical trials I think is one of the most important issues

to tackle. And our working group talked about that because one of our objectives touches on that as well, and it looked like, you know, it was actually one of those areas that was green, that there was a ton of funding, but it hadn't come out yet.

And then we started really looking at all of the studies, which I mean there wasn't anything wrong with the classification. I'm not saying that. But they were somewhat tangentially really related to the question of developing a sensitive assay that could be used, say, in a pharmaceutical trial or any other kind of clinical trial. They just kind of -- they weren't really designed to do that, although they would bear on that question.

And our Group decided that to really make progress in this area, there needed to be targeted funding where the RFA explicitly said the purpose of this is to develop sensitive assays for clinical trials for autism. And that without that, you know,

we're going to get these kinds of studies that sort of translate but really haven't done the job.

Dr. Insel: Yes, Alice?

Dr. Kau: Actually, there is an active not RFA, but it's PAR targeting exactly what we were looking for. So we don't have set-aside, but we do have special emphasis panel review for those applications. So obviously, you know, it's -- if there are not many grants funded, it's just because it hasn't passed through the review yet. So --

Dr. Insel: So the Europeans are ahead of us. So EU-AIMS was put together to do just what you described. And that's a collaboration, public-private, that's underway. We brought them across the day of the shutdown, right -- it was October 1 -- for a joint meeting. We shouldn't admit that we were working on October 1.

Unidentified Female Speaker: We weren't working.

Dr. Insel: We weren't working. We were

just -- we were just listening.

[Laughter]

Dr. Insel: And it was all personal. That's right. Thank you. Good clarification.

To figure out whether we could through The Biomarkers Consortium here in the United States do something very similar. And that's moving ahead very quickly. So I'm quite hopeful that that'll be done in a way that's actually much faster than the NIH kind of “let's put out an RFA and wait 6 months, and a year and a half later, we'll have grants funded to do in 5 years.

So I think we'll get this moving. But you know, the fact that it's already going in Europe is very -- is very promising -- and they've got a lot of good ideas.

Idil, you get the last word.

Ms. Abdull: Oh, such pressure. I do want to just kind of comment on what Matt said, that I agree with him 100 percent in terms of children who are either classic or minimally verbal. That we dismiss them, and when

parents say what interventions and treatments should I get, we're always told, well, you know, that's just severe autism. There's not much we can do.

And so I want to say to the doctors and the pediatricians and the people that are in the education system, I think we owe, as adults, to give every child the opportunity to meet their best potential outcome. And I don't think we should be telling that.

And just to give my example of my son. He is now using the Proloquo2go program on the iPad, which CMS does not pay for. Hi, John.

[Laughter]

Ms. Abdull: And he's able to tell us his needs, and once he's able to give us directions. The other day he gave us directions using the iPad to go to the mall, to go to a playground inside the Mall of America. And you know, a couple of years ago, people would have said he just -- he doesn't know. It's just behavior.

And he's able to answer questions like who was the first President of the United States? Was it George Bush or George Washington? And he would press George Washington.

So I want to just, especially for Dr. Perrin, we need to tell the pediatricians don't dismiss these children that are not talking. They are intelligent. They are smart. They are capable of learning, and we need to make sure, as adults, that we give them the opportunity to meet that. Thank you.

Dr. Insel: Yeah, so that's great. So just to sum up, I think there's been a really good discussion. I guess if I'm responsible for writing it up, I've got plenty of notes. I may want several of you to help me.

But this last point is really critical -- that when we put this in here originally in 2009, it was, I think, quite wise that we said which treatments and interventions, that there are lots of different kinds of interventions that can really change the

world of a child or an adult. We haven't talked much about adult interventions, but all of those need to be in Question 4.

And I think the sense of what we're hearing here is that there's a lot more that we can do on the process of how we do the science potentially, especially getting these outcome measures, getting predictive biomarkers or baseline measures, as a few of you have said, so that we can monitor.

I take Scott's point to heart that we have to be able to explain what we're doing and make sure that the public understands why this takes so long to do it well. But I think we've got some things we can point to from the last 5 years.

Clearly, technology is going to go so quickly here, as it -- again, maybe not with autism label -- but generically, the ability to develop whether they're social prosthetics or sensors or a whole bunch of things that can be really critical for people with the label.

So we'll try to capture all of that in the final write-up all within a page or page and a half, but I think we can do -- do some of this justice.

Let's go on to Question 5, and --

Dr. Susan Daniels: David Mandell is on the phone.

Dr. Insel: And yes. So this one, David, will you be able to help us with this remotely?

Dr. Mandell: I will do my best.

Dr. Insel: I'll read this. I don't know if you're looking at the slide at the same time.

Dr. Mandell: I am.

Dr. Insel: You are? Okay. So I'll just say welcome, and the question on the table is, "Where can I turn for services?" The aspirational goal is -- I'll let you read that. And again, we're going to want to try to capture not only the needs, which is what we have on the slide, but also what's changed over the last 5 years and what has our

investment delivered in terms of returns and outcomes?

Dr. Mandell: Okay. Thank you. And I think this conversation really fits hand in glove with the discussion before about treatments and moving demonstrated efficacious treatments and other kinds of services to the community.

So the aspirational goal for this question is, "Communities will access and implement necessary high-quality, evidence-based services and supports that maximize quality of life and health across the lifespan for all people with ASD."

We had a very rich discussion in our Group about the extent to which the objectives have been met. I think there's a general feeling of optimism and enthusiasm about what has happened over the past 5 years. I think when the IACC was having this discussion 5 years ago, there was very little going on -- very little research going on that was -- that it was -- categorized as

falling within this Question.

And certainly, if you look at the extent to which recommended budgets were met, that that's very different now, and I think that the field has matured considerably, and that maturing is really represented in our recommendations.

I think a big issue was health disparities, and there is a feeling that we have now done a lot of observational studies of disparities in care for people with autism and that we are ready to move from observation to action, to experimentation. And so there really was a recommendation that -- that -- we continue to address this issue and that we address it by moving toward experimental design to determine what kind of strategies best meet the needs of people who traditionally are underserved.

And does -- one of the analogies used was -- does a rising tide lift all ships? That is, do we need -- is this a geographic disparity that we can address by improving

services in traditionally underserved areas, or do we need to develop programs that are more culturally, ethnically, and racially specific than what we have now?

There was also a big interest in scalability, and this will be a theme when we talk about adults as well. But there is a lot of concern that we have funded a lot of programs that have shown efficacy or even effectiveness with very small groups of people and that we now need to think about what the issues are related to scale-up and how we think at the population level and at the system level about implementing programs that will have much broader effect.

To that extent, there are already groups that are -- that are -- doing good work in the community. We often talk about the research-to-practice pipeline, but there are a lot of people who can't wait the 5 years for that randomized trial, and so -- and are doing things in the absence of evidence, but they still may be getting very positive

outcomes. And we need to be partnering with them to examine the effectiveness of what they're doing and think about its potential for replication or for tweaking.

And to that extent, we need community partnerships. Most of the work in Question 5 is done well when researchers partner with community organizations or governmental agencies, and it would be wonderful to see financial support for those partnerships so that we can extend them, strengthen them, expand them, and start to think about how you effect change not just with the kid in front of you, but at the district level or at the health system level.

Related to that and related to some things that were said before, there are many, many natural experiments that are going on. And States, often in response to political pressure, sometimes with evidence to support what they're doing and sometimes not, are engaging in policy and regulatory and practice changes to meet the needs of people

with autism.

We need to be able to rapidly study those and not just a single one, but the multiple ones that are going on across the country. And that in meeting our objectives, we should be taking advantage of those natural experiments.

And I think a last thing, which is -- which relates to many of the things that have been said, especially for Question 1 and for Question 4, as we are doing this and as we are successful, we need to develop and disseminate what we're learning in a way that effectively reaches the public much more quickly than our journal articles tend to.

And I will stop there because I'd like to give a lot of time for the other people who were on the call to share any ideas they have about these objectives as well.

Dr. Insel: Thank you, David.

Let's see, who else was involved on this Group? Scott and Brian. So you want to start, Scott? Brian, you're on.

Dr. Boyd: Okay. I hope I have my thought ready. I think that everything we talked about is when you're going to engage in sort of systems-level change work, you have to think about the methodology you're using. And so we know some stuff from public health and other fields that are using implementation science to help us think about how to move evidence-based practice into community settings. So thinking about those kinds of funding opportunities, the pooling of the methodologies.

The other one that's being used to look at large-scale educational initiatives is improvement science that's being done at the Carnegie Foundation. So how do you work with large systems, in this case school systems, to help them think about how you quantify the issue so you can measure the outcome and design a series of iterative studies to address that issue?

So there are methodologies that are out there to help us think about systems-level

change and how to measure that.

Dr. Insel: Is that sort of the practice-to-research idea?

Dr. Boyd: Exactly.

Dr. Insel: Okay. Yeah, go ahead.

Dr. Borges: I was not on the call, but I'd like to make a comment because this is also relates to Question Number 4. I was just thinking on the disconnection that we were talking earlier about what is done in practice and what we have in clinical trials. And our experience has been that, for instance, there are a lot of small clinical trials that show promise with different interventions, nutritional therapies or even drugs, that then when we go to the larger scale clinical trials, they don't show the same kind of results.

And it is possible that because of the variability in the expression of autism that, well, we all know that there are different types of autism, but we don't really know how to identify the subtypes. But then we put all

these patients in the large-scale trial, and then many times these are small effects, and we either need huge number of patients or we don't see anything.

So I wonder if we need to find -- to discuss -- different clinical trial designs, different designs, not the regular RCT that we are used to deal with and do more, and this goes into this practice-to-research model more to community-based or more kind of effectiveness kind of trials. Because in the end, when we hear practitioners saying, well, we know this is not approved. We know this is. But it's working for my patient, and families say the same thing.

Well, they are kind of running their own clinical trial with very small number of patients. But then we cannot translate that in a larger scale. So how can we capture that in a way that is sufficient to convince all of us of the evidence or to build up into the evidence?

And I am aware, as I say that, that we

are the first one to have a lot of questions about this kind of design. So my thought is mainly, well, let's discuss other trials, other trial designs and see if we get somewhere.

Dr. Insel: Okay. Thanks, Silvana.

Cathy, and then we'll go around.

Dr. Rice: I think for both --

Dr. Insel: Before you start, is there anybody else who is on this Group who wants to expand? So we have -- you were on the Group? Okay. So you, and then we just want to capture the people who were on the phone calls first and --

Dr. Rice: Yeah. I think David captured everything very, very well. The only thing I think that we discussed in depth that wasn't captured was the objective on dental health and that we wanted that to be much more broad, about health issues across the board. It seemed very specific.

But another point that relates to both the discussion we've been having here and the

question before is, you know, we're looking for these group outcomes of groups of autism in randomized controlled trials. And I think one of the things that we're learning is to look backward somewhat in that behavioral intervention; the evidence for behavioral intervention was really based on individual -- individual-level -- studies looking at very specific functional targets: What behavior are you trying to impact?

And you add that up, and that works for that individual behavior. But if we put all those individuals together in a group summary, we may not be getting the same effects that we get. And so all this to be saying in terms of when we're looking at outcomes, you know, moving away from the autism as an outcome, IQ as an outcome, adaptive behavior, in and of itself, and looking much more at functional skill outcomes.

So can we group people together in terms of those that are minimally verbal, that our

outcome is really to learn a certain number of functional words? And group people in that way in terms of the functional skill areas that we're trying to address as a way of subtyping?

So we think -- you know, we try to find within the groups the magic subtype that people are going to be -- that are going to hang together. But if we do very good, specific functional assessments of where is this person in terms of their ability to communicate and their ability to interact and their ability to care for themselves, and then within those functional skills can find common groups and look at treatment groups based and change based on that way of hanging them together, that may be helpful.

Dr. Insel: So you know, I think the question on the table for us is we spent $123 million over the last 5 years to try to answer "Where can I turn for services?" And it's going to be important for us as a group, but also for taxpayers who gave a lot of that

money, to know what we got for that investment.

So I'd love to hear what happened since 2008, having spent the money, what did we get? Jim?

Dr. Perrin: Tom, I'm not going to answer that question.

[Laughter]

Dr. Perrin: And I apologize. I'm part of this Group, but I wasn't on the call because I was out of the country and, therefore, didn't have the benefit of the discussion. But I did want to put this a little bit in context.

Because I think, number one, we're seeing major changes in how we're delivering pediatric care around this country that have some real implications for kids with chronic conditions, including autism spectrum disorders. But we are really moving much more rapidly toward community-based teams of providers rather than individual physicians or groups of physicians doing their things as

doctors alone.

And I think that the move toward teams will allow much more attention to early identification, to really management of chronic conditions much more effectively in practice, and to linking kids and families to community resources much more effectively than we've been able to do up to this point. That is happening now.

We have tons of experimentation around the country. We're trying to bring that to scale at this stage so it isn't just a lot of really very exciting experiments, but rather really is something that is the tradition in pediatric practice nationally.

And there are some issues there that are really critical to moving forward with that. One is the payment systems, which many of you have complained about appropriately, are really framed around a traditional fee-for-service arrangement, which is not supportive of the kind of care kids and families need. It's that simple.

And unless we can move really toward some form of bundled payments or some other kind of arrangements that are really in law through the Affordable Care Act, but moving, quite frankly, slowly, unless we can move to that, we're going to have a lot of trouble really implementing this model of integrated, comprehensive, community-based care for families.

The ACA, by the way, also includes the notion of specialized payments for what is called "health homes." That's really designed predominantly for people my age who have multisystem disease, our fragile elderly like me. But in fact, we are trying to convince CMS and others that that's a really relevant concept for children with chronic conditions such as autism as well, and that will also help us provide that kind of thing.

And the last thing I want to just comment on because it gets back to some of the costs of care issues and the costs of having a child with autism that is really in

the background materials at least, and just to recognize that there is a lot of commitment in this country right now to short-term savings, savings within 3 years. And frankly that's not relevant to kids with autism.

We're talking about savings that are in the long term. We're also talking about savings to families by having better services for their children, making families be able to do their own jobs and business more effectively if their kids are getting the right kind of care today.

But the short-term savings that you can get with a frail, elderly Medicare patient like me are not available to children, and we must change the value proposition for children to talk about long-term outcomes as well as household outcomes effectively.

So those are some areas there. All of those are amenable to really imaginative, both comparative effectiveness research and health services research, as well.

Dr. Insel: Okay. But I think that's helpful, and what we're trying to capture is what is changing? What's new? What do we need to be pointing to as progress, and what are the continuing needs?

We're going to go right around this side. So Aubyn?

Dr. Stahmer: Yeah. It was hard to change my mind from the things we need to do to what we've done, but I'm going to try.

I think that people in the community are thinking about evidence-based practice now. Whether they're doing it correctly or have the tools, I don't know. But school districts and community providers and developmental services agencies are looking for that, and I think that's a result of the research that's been going on and the systematic reviews that have been done over the last 5 years.

Things like the National Professional Development Center on Autism have available to anybody for free ways to learn about the evidence-based practices that the research

from this organization and others has done, and I think that's a huge step from where we were 5 years ago. I can go online and learn about any of the evidence-based practices with videos and Fidelity of Implementation forums and lots of ways to learn about it.

Now could I go and implement it? That's another question. Probably not. And so I think our next step is figuring out best ways for training and sustainment of training over time.

The behavioral interventions are not easy, and I think one of the challenges we have in our clinical trials is that we train someone in a community to do an intervention, and then we measure the kid's outcome right after that. And sometimes it takes a couple of years of practicing the intervention before you get that good at it.

And so those are our challenges. But I do think there's a lot more availability and information about not just practices that people are trying to make money on that don't

have an evidence base but also the evidence-based ones.

Dr. Insel: Right. Geri?

Dr. Dawson: So this is what have we learned, responding to your question. So three quick things: One is that we have completely redone the economic analysis of the cost of autism.

Dr. Insel: David, you can hear this, right?

Dr. Dawson: That's been updated.

Dr. Mandell: I can. Thank you.

Dr. Dawson: And as David well knows. And then, as David also well knows, we have a much better, richer understanding of the impact of autism on families from in terms of their health care experience, the economic impact, and how that relates to ethnic disparities.

There's a new generation of studies that are coming out now that are being conducted in the schools. So Connie Kasari is a good example, where she's taken an intervention

that was developed in a lab and then implemented it in a school setting in a randomized clinical trial fashion. Or the work that Aubyn has been doing, also taking again lab-based interventions and then translating them into community settings through a train-the-trainer model, if I'm capturing your work properly?

And then the third thing that I think you were actually alluding to, but I'd like to make explicit, is that there has been a lot of work being done on developing Web-based training programs for dissemination of best practices in early intervention at -- to -- the States. And this has been headed up by Sam Odom in particular, who has -- did -- a complete review of what are the evidence-based practices that exist and then developed training modules that then are being -- and a whole training model that is being -- implemented in several States.

So there really has been some, I think, nice advances there.

Dr. Insel: Thank you. Alison?

Ms. Singer: So I just want to expand on one of the points that Geri just made, which is that we've learned over the last 5 years that efficacy in a lab-based clinical trial does not always translate to effectiveness in practice where our children go to school or where they're getting intervention in settings where the intervention is not being delivered by a white-gloved Ph.D. psychologist.

But that in the real world, our therapists are underpaid and far and few between and are not able to match the delivery that we've seen as far as the delivery in the clinical trials. And that there has been improvement in the work that Connie has done and that David is doing in moving these trials into community-based settings where the intervention has to be provided by the staff that is in the school.

And I think one area where we have to focus going forward is we now have to

translate that into research that we do for adults and realize that we have to start to study best practices for job coaching and adult support in the places where adults spend their day. So actually going out into employment settings and conducting trials in those settings so that we get the value of real world.

Dr. Boyd: Just to expand on that, I think we are beginning to learn a little bit that when -- I'm going to go with school-based because that's what I've studied -- school-based practitioners implement interventions well, that we can produce good outcomes for children.

I think one of the things that we don't know are some of the basics. So, so these are autism-specific treatments. A while ago, NICHD funded a childcare quality study around typically developing children. We learned a lot. We learned that basic structural variables like teacher education, teacher experience, adult-child ratio don't make a

lot of difference in children's outcomes.

But some of the process-oriented variables, like teacher-student interaction, sort of has more important or shows better outcomes for both children's social and academic gains. We don't know about quality of the school environment, where is where 3- to 22-year-olds spend a lot of their time for kids with autism.

So do those same variables hold? Does teacher experience make more of a difference for these kids? Do teacher-student interactions make more of a difference, given that there are qualitative differences in social interaction?

So we don't know a lot about -- we can't recommend classrooms to families who are, like, what kind of classroom should your child be in, given these characteristics? We don't know a lot about the quality of the school environment. So we don't have that foundational information, although we know that they're out there doing something

already. So --

Dr. Insel: Idil?

Ms. Abdull: I was also on this Group, and we talked about, you know, if you look at the question, "Where can I turn for services?" So, for example, for families, they have to understand where the services are, first, before they can even go seek it.

And we talked about how HRSA funds State autism implementation. They have grants. And I don't think even enough States do it. So we said that that was a gap. We need to have maybe all of the States or a majority of the States to have that. And what that basically -- and Minnesota doesn't have it either.

But Laura can correct me, what that basically is, that is that the State is able to get this funding from the Federal Government and is able to coordinate between the health, the Medicaid, and the Education Department and then also educate the families. So then they have family-to-family grants so then you tell the families what the

services are. Because if you don't know what the services are, it's very difficult for you to get it.

And we also talked about training. The LEND program -- there is also the LEND program-- so that training professionals to become autism professionals. You know, training young people to become autism professionals.

And we also talked about in terms of just over 35 States or even more having just parents advocating to change policy and saying we want early intervention and not really waiting for the Government, for the Federal Government. Just going to their State legislators and saying, "You want our votes? You're going to pass this law."

And parents using their voting power, including Minnesota, where we were able to get autism services covered up to age 18 just this year. And so I think this is one of those areas where parents just took, you know, the bull by the horns and said we're

going to do this regardless of what the Federal Government is doing or not doing.

And finally, in terms of services, I think there are a lot of things, especially one thing that I am really curious about, is that where we are with the wandering and the elopement. We know that's a problem, but we don't have a mechanism for these families and these children. Where do they get the services?

Who pays for this tracking GPS system? I'm sorry again. The CMS does not pay for it.

[Laughter]

Mr. O'Brien: Show us where we have said that.

Ms. Abdull: Well, in Minnesota. In Minnesota, a child has -- the doctor says that there is this child wanders off or the education system says that, and it's on the IEP, and you go to the doctor, and the pediatrician says it does. Medicaid or medical assistance, we call it in Minnesota, they don't cover it.

Dr. Insel: So let me -- let me break in because time is short, and remember the question on the table is our scientific investment has been $122 million over 5 years. I think we need to be able to report out what we've gotten for that investment, and I'm sure there are lots of needs that are unmet.

But the money has gone out there. So can someone help explain? Geri mentioned a few things and Alison as well. We've gotten a -- but I think for David's purposes, I hope, David could probably benefit from a really succinct explanation of what we have now based on the science on services that we didn't have in 2008 or '09.

Scott?

Dr. Mandell: Tom? Oh, sorry.

Dr. Insel: Go ahead. David, did you have a --

Dr. Robertson: Does David want to say something?

Dr. Mandell: I was just going to

potentially offer that -- offer a starting point for that succinct description based on the objectives that we set out. So we have a much more sophisticated understanding of disparities in delivery of care to children and adults with autism, and we know now that it extends beyond just age of diagnosis, but also to the treatments that they receive.

We know that self-directed care for community-based services is feasible. It's possible, and it can result in more positive outcomes, although we still need to figure out how to bring it to scale. We know that we can take evidence-based practices and with appropriate training and supports have community clinicians implement them in a way -- in the way that they were designed and achieve outcomes that are similar to what we observe in lab-based settings.

We know that the mortality of people with autism is not that different from that of typically -- of their typically -- developing peers, although there is some --

there is some decreased life expectancy among them. But it also points to the needs to address geriatric and older adult issues with individuals with autism.

We don't know as much about cost-effectiveness as we -- as we need to -- although we do know a lot more about cost than we did. But we still need to push in this -- in this particular area. And we know that we can train individuals who are working in the community to work successfully with people with autism. We also know that we don't currently.

So those are the things that I would -- in sort of a brief summary of the last 5 years in this area of research.

Dr. Insel: So the only thing I would add that we heard around the table was the impact on families. We've done a fair amount of work on that, and Geri has one other thing to add, too.

Dr. Dawson: I think in terms of deliverables, so to speak, in this area we

could also put the first empirically supported physician guidelines for the treatment of GI conditions, sleep conditions, and ADHD, which I think was a major, major step forward in terms of defining standards of care.

Dr. Insel: David, would you agree with that?

Dr. Mandell: Oh, I think, yes, absolutely.

Dr. Insel: Okay. All right. I feel like that's a good list. Scott, go ahead.

Dr. Robertson: So just before I mention a couple of comments on this, I just wanted to say briefly what was mentioned before on the Affordable Care Act, just one thing to add, and I know we don't have time for a discussion for a couple of months. But there are nondiscrimination provisions in the Affordable Care Act.

So hearing all these stories where folks can't access health care services at times that they need to is really, really, really

highly concerning to me because of the fact that, you know, it's protected under the law that you can't say, well, you're autistic, you can't access so and so health care services, that they make distinctions in service provision.

But to dovetail back to Question 5 here, on what have we been learning, one of the things that was mentioned on the call that I think David pointed out a little bit is that the objectives are sort of worded in a way that may be obscure as being able to see some of the gains we've had.

Some of these objectives, and maybe that can be enhanced in future plans, some of these objectives are way too specific, like getting toward dental care. We really want broader medical, kind of health care access. And some of them are way too broad, and we can't tell whether we've made gains in that area because they're just too general.

And we've also had a constraint that sometimes accessing, say, when some

innovative supports and services are happening around the country in home and community-based services and other community-based services, not always able to access data and connect, you know, have that connection to the community for getting research is something pivotal that was mentioned a little bit on the call as being able to have that connection.

And that reverberates back to that ongoing theme of that action of research and community connection on research and having the community both being something we can be doing research on from and then advising and providing input and teach them about what's going on, too, to dovetail a little bit back to what Scott had mentioned previously about making sure folks are educated on what gains we have made in supports and services. We're not really good at doing that with the dissemination part. So sorry if I said too much there.

Dr. Insel: No, that's great. I think

that's a theme that's emerging from all of these questions. Again, it's one of those cross-cutting issues like the one that John brought up at the beginning of the day.

Can I go back to the first thing you said? Because I'd like some help from the -- especially from the IACC members who are here. In this report, it seems it would be sort of neglecting reality to not say something about the Affordable Care Act and mental health parity and all of these things that are sort of historic changes in the ecosystem, even though it's not -- you know, we don't have a research base for that.

But to sort of neglect it would be, I think, conspicuous, would be bizarre not to say something. How best do we deal with that? What would be -- because this is about research, but is there something, some way to fold that in? Geri?

Dr. Dawson: I would say that it would be important to mention both the State coverage of insurance for early behavioral

intervention, as well as the Affordable Care Act. And without the studies that have been done that have shown the efficacy, and by the way, we just barely made it, you know, in terms of crossing the line of efficacy, we never could have made the argument for insurance coverage at the State level. That's huge.

That's a major transition in terms of aspirational goal. And I think, similarly, it's the modicum, but at least some existence of efficacy around behavioral health treatments, which I think Zach and his team have done such a great job with the systematic reviews that are going to allow us to take advantage of, you know, expanded mental health care under the Affordable Care Act.

Dr. Insel: David, are you okay? I mean, is there a way that you could embed this in the commentary? It just seems like we have to reflect on it in some way, and I think what Geri just said is maybe a way to explain how

the science had an impact on policy, which is what the aspirational goal is here.

Dr. Mandell: Certainly it could be folded in. I guess it's sort of struggling with the directive given to the IACC related to research and how -- I mean, I would be happy for it to be expanded to address these issues as well, if you feel that that's appropriate.

Dr. Insel: I mean, maybe one way to do it is toward the end of this section to just describe, in addition to unmet needs, to describe some of the impacts that the research is having outside of the scientific community.

I wonder if that would be the best way to frame it. John, what do you --

Mr. O'Brien: If there would be some way to be able to link what you're proposing to what ASPE is proposing, the Assistant Secretary for Planning and Evaluation? Because they have been and will continue over the next several years look at the changes

that were made in insurance coverage, both because of the interim final regulation in 2010 and now from last Friday.

So you know, to the extent that there could be some connection with this group and ASPE to have an ask, I think that could be helpful.

Dr. Insel: That's very much consistent with this idea of practice to research. So building in, baking in some kind of scientific process as the policies begin to change to know what's working. And like it or not, we're going to have 50 experiments going on that each have some slight difference to them.

Nancy?

Dr. Larry Wexler: Hey, Tom. This is Larry Wexler.

Dr. Insel: Great. Go ahead.

Dr. Wexler: Thank you. I just wanted to comment briefly on some of the statements that were made about the difference between clinical trials essentially with I believe

the phrase was "white-gloved psychologists" and the reality in the classroom.

OSEP used to devote $20 million a year in model demonstration projects, and these were to do exactly the -- to take research that was conducted in clinical situations and bring them into realistic environments with realistic people conducting them, essentially into schools with teachers and to develop models based on that.

When our money went to -- our research money was transferred to -- IES in 2004, IES does not view that as a gold standard research approach, and they do not do model demonstrations. We've retained some research authority and have done some models, but our funding is extremely low for that. And with the shrinking sequester budgets, as I'm sure you're facing at NIH, the likelihood of us being able to do that is less.

So in terms of the IACC, you know, I certainly think that one of the purposes of this, if not the purpose, is to coordinate

research, and I think that the idea of focusing research or some research on actual model -- developing models -- for implementing research, especially instructional and behavioral research, in actual schools and classrooms where -- and I realize this isn't adults, but I work for, you know, a school-age group -- that somehow that this be coordinated and be undertaken, you know, amongst all of the agencies that do research around autism. And we'd certainly love to cooperate and collaborate, but I think it's something that the IACC ought to address. Thank you.

Dr. Insel: Thanks, and of course, we're about organizing partnerships beyond Government as well.

Nancy?

Dr. Minshew: Not to overlook the obvious, but I think certainly we've seen a much better documentation of prevalence, and that has led to much greater awareness by the public, much more support, and awareness of

the need to do something. And then, of course, if you watch the prevalence studies over time, you can see that in the communities, there's a growing awareness.

So that now that the teens, the teenagers, that were missed when they were younger were being picked up in the last CDC study. So I wouldn't underestimate that impact either.

Dr. Insel: Okay. I think, again, for David's purposes, to the extent to which we can quantify that? I don't know how to quantify awareness, but we are going to need to put numbers around all of these impressions if we want this to be a tight document.

And so if you can help us think about where the data might be that we can cite, that will be -- and especially if you can say this is where we were in 2008, this is where we are in 2013 -- that's really what this document needs to look like.

And I think we have a list of pretty

good examples. Whether it's cost or family impact or some of the things David mentioned, we can do that.

Coleen, you want the last word on this one?

Dr. Boyle: Thank you. Thank you. I was just going to say we do track awareness through some of our panel surveys so, and we could use that as data. I don't remember what the data say, but I know we do track awareness.

Dr. Insel: So what years do you have? Do you have --

Dr. Boyle: Ah, I'd have to go back and see, but it probably covers this time period.

Dr. Insel: So would you have something from 2012?

Dr. Boyle: Probably. It's pretty quick data.

Dr. Insel: Okay. Good. That would be great to know, if we could get that.

Last comments on Question 5? I think this Group is getting tired, but I don't want

to give you a break until we get through this next question because --

Dr. Paul Shattuck: Hey, Tom?

Dr. Insel: Yes.

Dr. Shattuck: This is Paul Shattuck.

Dr. Insel: Yes. Oh, hi, Paul. Great. Any further thoughts or comments here?

Dr. Shattuck: You know, maybe my comment could be kind of a bridge between this question and the next question. I apologize. Really, I have to swoop out in a few minutes, and I'm terribly disappointed I'm going to miss the bulk of the conversation about adult stuff. But if I could only make one point in this whole meeting, this is the point. I think it ties the two together.

You know, most of the breakthrough work on human development in recent decades has been preceded by measurement innovation, and we've heard a lot about measurement this morning and this afternoon. You know, the development and refinement of fMRI technology, you know, paved the way for

countless breakthroughs in neuroscience, breakthroughs in gene sequencing, and microarray paved the way for breakthroughs in discoveries about the role of genes.

One of the reasons ABA is so successful is because ABA providers are really good at measuring fear and measuring the results of interventions.

Now let's talk about social services, service systems, programs that are not really clinical treatments, but things like adult services and employment supports. Let's talk about the unemployment rate or quality of life at the population level. Where are the measurement breakthroughs? Where are the investments in measurement methodology innovations? You know, there are some little bits of effort here and there, but this effort is really lacking.

So just as an example, I did a back of the neck estimate, a very conservative estimate I would say, that we spent about $12 billion last year on special ed services for

kids on the spectrum. So we're doing lots of stuff to help people on the spectrum, but does it work?

Are we doing the right stuff that meets the needs? Has quality of life improved? Are today's high school grads on the spectrum more or less likely to go to college, to get a job, to have friends, compared to their counterparts 10 years ago?

We really have no clue, and we can't tell taxpayers or the autism community what we got in return for that $12 billion spent on special ed services last year. And that's just the tip of the iceberg, not even thinking about Medicaid.

So I would just venture to say and conclude for this point that what we don't need is "more research," because I think that phrase is just too meek and tepid. What we need, in my opinion, is an obsessive preoccupation with measuring results in ways that are relevant for policy and program decision-making.

We really need a revolution in social indicators and program-level measurement. We need a giant leap forward in methodology for measuring needs and outcomes at a program level, a community level, a State level, and a national level. And measuring at the clinical level is certainly important, and I don't want to take anything away from the extensive conversation about developing clinical measures. But measurement challenges don't end with developing a new scale or tool for use in a doctor's office.

We need measurement systems that can roll up to the program level, the community level, the State and national level. That will be the key that opens the door to some of the practice-based evidence dreams that David alluded to earlier. They will open the door to building an evidence base as we go.

And if I can only ask one thing of IACC, it would be to prioritize investment in the development -- basic research on the development -- of social indicators and

program-level indicators and system-level indicators. And if we don't do that, then we're going to meet again here in 10 years, and we'll have a lot of cool brain pictures and RCT data about behavioral intervention's efficacy, but we won't be able to say what the unemployment rate is.

We won't be able to say whether we've made meaningful improvement on the quality of life for people on the spectrum and their families, whether it's getting better or worse over time. And I think that would be a shame.

Dr. Insel: That's terrific. We shouldn't allow you to leave. So can you spend another couple minutes with us?

Dr. Shattuck: Yeah, sure.

Dr. Insel: So could you just unpack this a little further so we're all clear about what you mean by program indicators and social indicators?

Dr. Shattuck: Yeah. So by program-level indicators, you know, my background prior to

academia was working in the nonprofit sector. And you know, in the nonprofit human services, you deliver program-type services, not necessarily clinical interventions.

A lot of the stuff that we do with kids and adults and families are not necessarily clinical interventions. A program-level measure is a measure of the process, you know, what's delivered to whom, and what are the short- and long-term outcomes of delivering those services.

So for example, vocational rehab services. Do we have -- we still don't really have good indicators about the benefit and the long-term impacts of the provision of job coaching, for instance. You know, we have some isolated studies of small intervention efforts, but we don't have data at the community level or the State level. We can't say is, are outcomes better in community A or community B?

You know, measurement, there's a measurement revolution happening in corporate

America, in some sectors of public administration -- the ability to measure results and understand whether change is occurring; our ability to do that is expanding exponentially in so many areas of our society. But oddly, to me, in this, we need -- we need -- an infusion of some of that energy and some of those ideas, I think, in the world of autism services research.

Dr. Insel: The last question, Paul. Is there an example from the last 4 or 5 years that you could point to that would be a good model that you'd like to suggest gets emulated or scaled up or at least gets studied in greater detail?

Dr. Shattuck: I think that -- I think some of the work that's being done in the area of community development, you know, some of the work on collective impact and measuring change at the community level for initiatives; they're trying to increase high school graduation rates in vulnerable communities. I think that's worth taking a

hard look at.

I also think the Mental Health Service Research Conference a few years ago showcased some really cool initiatives that are happening in mental health service HMO settings, where there's an attempt to do clinic-level measurement that's meaningful for the doctor-patient level decision-making, but it can also get rolled up at the system level to understand how things are unfolding in terms of the quality of care and the outcomes of investments made at the HMO level.

Dr. Insel: Okay. Any other issues on this? Because we'll move on to Question 6. Actually, I think you've taken us into Question 6. So, and David, you did such a fantastic job on Question 5, I think you're going to do Question 6 as well.

Dr. Mandell: Okay. It's nice when the aspirational goal is just laid out there for you. So all right. So the aspirational goals for Question 6 are, "All people with ASD will

have the opportunity to lead self-determined lives in the community of their choice through school, work, community participation, meaningful relationships, and access to necessary and individualized services and supports."

So to try and follow your request from before, Tom, in terms of what we've accomplished, I think there is a much better sense that than there was 5 years ago, at least among the research community -- and obviously, this is something that families already had -- but that autism does not end at 18 or 22 and that there has just been much more research and publications in general on adults and the needs of adults with autism than there was 5 years ago.

There has been increased effort to figure out the best ways to measure quality of life for adults and to think about their needs within the context of the community as it relates to education, employment, housing, and health care. But almost every -- every --

objective within Question 6 did not meet its funding goal over this period.

One of the challenges that our Group ran into was the extraordinary overlap in the objectives and that very often the outcomes were the same for each objective. That is the thing we were supposed -- that researchers -- should be focusing on, and there was just a slight variation in the context in which they were trying to do it.

One of our thoughts was that we really need to unpack that first objective related to employment, postsecondary educational opportunities, community inclusion, self-determination, relationships, access to health services and community-based services. And we ought to be thinking about each of those things individually.

And this actually ties very nicely into Paul's comment about issues related to measurement because one could think of each of those things as potentially providing an indicator of the overall success in improving

care for adults with autism. We certainly felt like the jury was out when it came to figuring out how to measure quality of life in adults currently.

That there are not State-level -- there's not State-level coordination of services, and there has been no study of strategies for State-level coordination of services. But this is really an area in general for adults where we have a lot more work to do.

And I actually, at the risk of putting him on the spot again, wouldn't mind yielding the floor to Paul again because I think he has some really important frameworks for thinking about adult services and where we should be going as a field?

Dr. Shattuck: Thank you, David. I'll do my best. I wasn't prepared for that.

But -- well, yeah. So some of the work we've been doing basically documents descriptively, you know, things aren't turning out too well after young adults leave

high school across a range of these domains. As far as where are we going next, I do think that measuring quality of life in this population, that there's definitely room for growth there, and I would support, you know, resources being devoted to try to understand from a -- from a community-based perspective -- what are the outcomes that are meaningful to young adults on the spectrum and their families.

You know, PCORI might be a good mechanism for doing some of that kind of work. So be thinking about bringing the tools of the patient-centered outcomes measurements and development strategies to the task at hand.

I also think that we could learn a lot by importing some of the ideas and methodologies from systems science. I think it's interesting that we talk about systems of care all the time. We talk about the adult service system and the school system and the community system, systems here, systems

there, everywhere are systems.

But we don't really avail ourselves of the tools of how to think about systems and how to analyze systems that are pretty richly developed in other disciplines. And I think maybe we want to be looking at ways to bring in expertise from some of our allied public health and systems science fields to help us think a little more clearly about the systems-level issues here, both at the adult level and the child level.

Dr. Insel: There are a lot of hands thrust up in the room here. Before we go to the people around the table who were involved in some of these discussions, I just wanted to remind you that it may be late in the game, but we -- NIMH has recently released a series of RFAs in just this space. So it's to fund research on transition to adulthood and on access to services to support independence and foster community engagement in adults.

And -- amazing response. Seventy-eight applications came in over the last couple of

weeks. So we're hopeful that this will be an area where we can have some impact, but you won't see that for a little while. Won't happen right away.

Idil and then Scott.

Ms. Abdull: So I was also on this Group, and if you look at just the question, "What does the future hold for adults with autism?" I would say not much. It's bleak, the future. And because we're not ready for them. These children do grow up.

And as one of the moms in the public comments said is that the big -- one of the biggest things that we worry about as parents is that what's going to happen to my child? Is he going to have housing available? Is he going to be able to go to college if he wants to? Are there colleges ready? Are there employment ready?

So in terms of employment, we're not ready. In terms of housing, we're not ready. In terms of waivers even, how many States out of the 50 States have autism adult waivers?

Not many. You can count them with one hand or maybe just couple of fingers.

And then also I think Scott has mentioned this, maybe last year at the congressional hearing. There isn't the ability if you have a waiver in one State to move it to another State. And if -- I don't want to speak for CMS again, but if I understand it correctly is that waivers are half State funded and half Federal.

So while SSI, for example, you can move to another State, but when you have -- because that's only federally funded. But for the State part, if Minnesota had the funding, California might not have the funding. So that makes it difficult to move. And I think a lot of parents don't understand that.

And so and then housing. There are people who would fight group homes, who would say we don't want to seclude these people. There are people who would -- but then where do you take them?

So I just -- I mean, Scott -- I'm glad

Scott is speaking next to me, but as a mom whose kid is 11 now, and it's the one thing I worry about the most. What's going to happen? Who will take care of him? What housing? What will happen?

And I just -- as a society, we are not ready, and I think we're failing them. And this is one of those things that I don't want to wait for some research that's going to take years. No offense, Amy --

[Laughter]

Ms. Abdull: -- or decades to tell me what's going to happen. I want to have it now so I don't have a heart attack worrying about it.

Dr. Insel: And again, just to frame this discussion, these are critical issues. It's not clear that they are research issues as much as policy/services issues. And as I've said for 2 years, we need a separate initiative around those problems because they are so difficult and so important.

I'm not sure they'll get fixed when we

just really talk about what we need to talk about here, which is what's the science? What science has been done? What science needs to be done?

Scott?

Dr. Robertson: Yeah, and I'm agreeing on the not much. If you look on the last several years -- well, just one thing I'd like to say at the forefront on this is I hope that when a more -- a bigger -- update to the Plan is done that autistic adults can be thought of across the board, across the whole Plan.

The fact that we pigeonhole it out to one question out of six, this isn't done in the rest of the developmental, like developmental disabilities and neurological disabilities where you're like, oh, we'll talk about kids for 80 percent of the -- and then, oh, you know, the last, you know, 30 minutes. Oh, suddenly, we're talking about everybody 18 and older.

You know, it's ridiculous, and folks spend, you know --

Dr. Insel: I'm not even sure it was there at all at one point. So --

Dr. Robertson: Yeah, yeah. Oh, I'm sure it's an improvement.

Dr. Insel: You're absolutely right.

Dr. Robertson: It's before I got on there. But we need to do better on that. I will say that the funding levels kind of bear out when you look at this, that this is atrocious that we're only spending, I don't know, about half or so. I counted up the recommended funding versus the funding that we actually spent. You know, we're only meeting about half that. And it shows that we haven't really gotten, you know, much gains. We still have major challenges across the board on employment, higher education.

There was a study last year -- the only study of its kind -- looking at health disparities that autistic adults face that one of my colleagues, Christina Nicolaidis, and some of her other colleagues out in Oregon had studied, for community-based

participatory research, actually going out in the community, doing surveys there.

And had found disparities in mental health access, just regular physical kind of health access for autistic adults for access to drugs, communication providers. You name it, across the board, the outcomes looked really bad, at least from the perspective of what they had found from the autistic adults.

Now given it was -- it was self-reported data. So they need to dive more deeply into that. It's only at surface level, but it's better than what we had before. We didn't know anything at that area before.

And related to that, and this does relate back to research directly, and I mentioned this -- I feel like I have to mention this all the time, and I mentioned this last year for last year's development of the Plan Update. And this does relate back to research because this is really real-world data gathering is needs assessments, which I consider research, really systematic

gathering of data on where the gaps lie.

We're not really doing that at a systematic level nationally and regionally in the way other countries are doing, in England and other places, where they've mandated really systematic needs assessments to be looking at health care access disparities. They're looking at employment across the board, not just be doing scattered studies on employment, et cetera, but doing really systematic ones in the way that, for instance, in Pennsylvania, a little bit for adults, but more so for children we have done systematic.

You know, the State government has done systematic needs assessments. But again, it was more focused on kids. But at least you could take the idea of what happened there and gather really extensive data on where the gaps lie.

Because it's really, it's harder to know what we should be doing in terms of making gains on supports and services when we don't

necessarily even know where all the real-world, you know, pitfalls and problems are and haven't gotten them quantitatively and qualitatively out in the communities, you know, nationally and really in depth regionally.

You know, I just -- it just bothers me, and I'm sorry if I'm being honest on this. But it just bothers me that England, and I said this before last year, but I'll just say it again for folks that didn't hear it. That England mandated in 2009 needs assessments in their legislation. That was 4 years ago, and they did it across their country and gathered a lot of data systematically.

And that was specifically for autistic adults. They actually passed legislation around autistic adults needs assessments and, you know, not happening here partly because -- and I know some of the limitations is that our -- the Federal legislation that empowers this body and OARC doesn't have adults written specifically into the language of the

bill, and it shows at times in the work that happens is -- I think there would be a priority more for needs assessments and more initiatives around adults if it was built into there.

But I think people could also -- I think at NIH and other bodies across the Government -- they could just empower themselves to be doing that work, even if it doesn't -- if it isn't mandated by the legislation.

Sorry if I jumped off on that, but it bothers me from the perspective of a lot of autistic adults out there and a lot of families and a lot of allies who are constantly saying, you know, why can't we have better improvements on this in research and -- research and practice and the integration of that?

I mean, I hear that all the time, and I don't know what the good answers are about the fact that we just -- I keep having to say we don't have data. We don't have data in the research sphere around adults. And I'm tired

of saying that. I want to see that change.

Dr. Insel: You know, it's a great point. And as you note, the portfolio analysis entirely bears you out, and the numbers speak for themselves.

Dr. Robertson: Yes.

Dr. Insel: That's why I started by mentioning this RFA in the hope that maybe it's 5 years too late, but we are putting funds into this and starting to move the dial.

Scott?

Mr. Badesch: Yeah, I think a lot of the things that you're trying to find, there's a part of this is a mindset in both individuals and families. I'm sitting here thinking that 5 years ago, the word "outcome" was somewhere out in my vocabulary, but not as great as it is today.

And I think more and more parents and individuals are defining what is needed by what is going to be achieved by what happens. And I think what Paul said is right on

target. But I would just caution that one of the issues we're dealing with adult services is because we have kids or young adults transition at 21, and they're just not ready for adulthood.

So how do we establish, you know, in the words of lifespan, what are the outcomes we want a kid to be at 3? What do we want him at 10, or for her, at 15 and 20? So that when they're transitioned into adulthood, we're able to do this.

The reality of the services for autism, at least to my knowledge, is no different than any other disability. I mean, I would also question that whatever we're doing helps all disabilities, but we have not seen the unemployment rate among adults with autism drop in 50 years. If anything, it's gotten worse. So you know, there are housing needs. So this is a critical issue.

The one thought I would say, and it's not to put blame on anyone, you know, if you want to talk about a public policy system

that's about as fouled up as possible, it's the rules regulating what adults can and can't do with funding or availability. You know, we have funds that will keep kids in a home setting, but we don't have funds to use those monies for something that may be more leading toward employment.

So our job coaches last X number of days, when we know if we could just get a job coach for an hour a day a week, that's good. So what happens is the kid loses a job, and then the Government funds tons of money to keep the kid in a home or the adult in a home. That makes no sense.

So I would just suggest on this goal that whatever you do, there has to be a complementary effect of how do we change these policies so there is more flexibility for families and individuals and agencies to work with achieving the outcomes Paul, you know, really wonderfully said.

Dr. Insel: Okay. Jim, and then we'll come around.

Mr. Robison: I expressed the view when we did last year's Plan that adults should be woven into all of the write-ups in the questions, and I would like to suggest to those of you who are writing up Questions 2 through 7 that you consider how we could weave the adult issues as applied to your question into the write-up of that question.

For example, for Question 1, I would propose to say this year something like in 2008, Question 1 was directed exclusively at the detection of autism in young children. In 2013 we recognize that detection concerns include older children, as autism was not correctly diagnosed initially or at all, and previously unrecognized adults, most of whom grew up prior to broad recognition of less severe autism.

And I think with that preface, we can then consider our progress in answering all of the various questions here in the context of both children and adults. And I think that we should do that because it's significant

that every one of the questions that was written 5 years ago was directed exclusively at children.

And I think, therefore, the responsible thing for us to do this year is to explicitly mention the adult perspective on that question by each person.

Dr. Insel: Jim?

Dr. Perrin: So I do think there has been a moderate amount of progress in this area, and Paul said it in the sense that we know a good deal more about quality of life measurement among young adults, not so much among older adults. We have some measures now of really functioning of mainly young adults rather than older adults and some association of that functioning with their services late in adolescence.

We don't have a lot of really good life-course research, frankly, in autism, the ability to really monitor trajectories effectively from age 3 to 5 to 10 to 20, which would be incredibly helpful to have.

That would be really good because I think have some studies that looked at 3-year-olds and saw what they were like at 25, but very little about the information in between.

Nonetheless, that's a real start. We do have some longitudinal data at this point about -- about young adults and functioning. I think two areas that I think we may want to continue to work on. There's been a little -- but one is also -- there's been a lot of work in transition specifically. Not so much in autism as has been in a whole bunch of other chronic conditions.

So we know more about what works and what doesn't work. Things like developing individualized planning, generally starting planning at age 14, not at age 18. The information about connecting earlier providers with later providers in the health care arena, especially that pediatricians should have a direct interaction with the family practitioner or internist and help that connection to exist. So we have some

data from transition, I think, as well, which has been different from 5 years ago.

Two areas I just want to comment on, though. One is that we still know -- we have a lot of unanswered questions about adolescence in general. We don't know a lot about really the pubertal changes, the impact of puberty on the mental health comorbidity conditions. We don't know enough about the effects of adolescence really and endocrine changes in autism and on autoimmune function. Some tremendously interesting areas to work in.

And then, finally, we do have -- I'm sorry to say, we do have a natural experiment developing that allows itself, again, to good comparative effectiveness, and that is the Medicaid expansion for adults, which is tremendously relevant to people, young people with autism, many of whom will be eligible for Medicaid expansions in the States. And we do have a number of States that have decided not to implement that expansion, and it would

be interesting to do some comparisons in States that do and States that don't.

Dr. Insel: The only thing I'd add, Jim, is it was mentioned before, I think by Nancy or someone, about the optimal outcomes, Debbie Fein's work on -- because that really speaks specifically to what does the future hold. And that, although we've had data in the past, I think that was the best of the long-term studies to show that, in fact, 20 percent of kids with potentially looser diagnosis.

So I'm going to go --

Dr. Perrin: The trajectories we don't have good evidence on. The actual --

Dr. Insel: We have before and after, right.

Dr. Perrin: -- patterns of care over time.

Dr. Insel: So --

Dr. Shattuck: Hey, Tom, this is Paul. May I weigh in?

Dr. Insel: Yes.

Dr. Shattuck: Okay. Paul Shattuck here.

These are great comments. I just wanted to raise, you know, bring it back to the research question. So what research could we do that would make a difference here?

The question is what's going to happen to my child as they grow up and age? You know, most parents that I have talked with, the big elephant in the living room kind of question that people hate to talk about but it's on everyone's mind: What's going to happen to my son or daughter when I die, when I'm no longer around?

You know, that's the ultimate sort of test of how well we've done as a society with our services and our supports and so forth. And I think the answer to that question is largely determined by two things that are studied a lot in the social sciences, and I kind of wish we had the National Science Foundation here on the part of the IACC.

You know, social networks and community, these are two topics that are studied deeply

in sociology and anthropology and other social science disciplines. And I think social networks and community cohesion are kind of the answer to that question of what's going to happen to my kid when I'm no longer around.

If my family and my child, if we have a rich social network, if we're part of a cohesive community, if we have -- if there are other people besides paid service providers looking out for my kid -- I'm going to be at more peace about that big question than if the only people looking out for my kid are some paid service providers where the turnover rate in staff is 50 percent a year.

And I think there are actually some really interesting -- there are some very interesting -- research in sociology in particular about the role of social networks in health. Actually, Dr. Perrin could probably speak about this. I mean, that's a life-course sort of revolution that's happening in maternal and child health

thinking these days. There is a focus on social networks, and there's certainly a growing realm of social network research and health outcomes.

But I would love to see that kind of on our radar screen as we think about future research -- is how do we move beyond thinking about clinical interventions and services and how do we think about building intervening at the level of social networks? How do we help people and families enhance their social networks?

Because I'll tell you, a lot of the families I know, they're kind of beleaguered. You know, by the time their kid becomes 20, 30, 40, there is sometimes a retrenchment where families become less connected because of the cumulative strains, the financial strains, the mental health strains of caregiving can really take a toll.
And I think that thinking about how to enhance social networks and develop community in meaningful ways through service provision

and community organizations, community-level interventions, I think that's -- that's one of the keys to answering this question, what is the future going to hold for my child? Thank you.

Dr. Rice: So I think one of the areas of progress that we have had is mining some of the existing population-based cohorts of the Utah-UCLA study, for instance, the longitudinal education. But those are based on old cohorts of what was autism.

And that one thing we talked about this morning is the investment in the infrastructure that we've been making in terms of population-based cohorts I think has yet to be realized for this objective. But I think it's something that we should see as some progress that we do have some population-based cohorts who are currently children and adolescents, soon to be young adults, that we should be considering for future studies to really look at needs and functioning.

Dr. Insel: Cathy, does that have to be U.S., or are there global cohorts that would be better?

Dr. Rice: Well, I think if we're talking about service provision and impact in the U.S., then certainly I think we should be focusing somewhat on U.S. But I think in terms of the characteristics of the population, the needs of the population of autism, that could be -- you know, the U.K. data, there's Scandinavian data that could be looked at in that way that I don't think we've really thought about in terms of adults.

Dr. Insel: Let's go around to Anshu.

Dr. Batra: Thanks, Tom.

You know, I wanted to make a comment, actually, more than a suggestion on what to do here. As I'm listening, again, I'm a pediatrician so I see little itty-bitty ones, and then now they're aging out. And I just see this as really a commentary on the natural course of development of individuals.

And, and you know, this -- I feel like this is almost on-the-job training. As our youngsters are growing up and aging out into the adulthood, we are learning what our needs are for these individuals. And I think of it from the standpoint of my son, who's 16, and when he was little, it was all about getting him to talk.

And then it was about, well, just having friends and having a happy life, and now it's, you know, we've shifted it to just, you know, having a skill set that will allow him gainful employment. And I'm sure, you know, 5 years from now, it will be, well, being able to live independently on his own at some point, hopefully.

So I guess, you know, I'm hearing this, and I'm thinking everything that people are describing are things we need. And again, I think we certainly haven't been paying -- you know, our monies have not been going to this area, but I think clearly over the 5 years, we're recognizing our kids are getting older

into adulthood now. We need to do it. And there's no shame in it. It's on-the-job training.

And I guess I wanted to highlight what Dr. Perrin had said, which is really the trajectory. I think we need better sort of information on the trajectories of the different developmental stages that individuals go through. We have a lot at 3. We have a lot at, you know, after 21, but nothing in between.

And I think that's just the nature of sort what we've been focusing on, and I think that in-between black hole, the adolescents are -- just like the adults -- the adolescents are sort of a forgotten breed. And I'm a mother of one in that, you know, forgotten breed, I have to be honest.

The issues that we have been facing with my teenage -- my teenager -- are so intensely intense as compared to my typically developing teenager, and I wasn't expecting it, and I wish -- and my providers don't have

answers for me as robustly as I would like. So I would like to see some more information and data collecting on those, on the black hole sort of population.

Dr. Insel: Typically developing adolescents are a black hole as well, I can guarantee you.

Dr. Batra: You bet. I have a couple of those, too. But you know, it is -- it is so challenging to deal with a teenager, but then a teenager with special needs it's even tenfold. The issues of anxiety and isolation and, you know, my God, puberty. I could go on and on.

And we just don't have answers. And again, as a practitioner, I struggle with the guidance for that population to --

Dr. Insel: We actually haven't discussed this very much in this Committee. Adolescence has not come up very often as a topic.

Dr. Batra: It really hasn't.

Dr. Insel: We talk about adults. We talk about young kids, but this is kind of the

dark matter of this -- of the lifespan.

Yeah, go ahead, Scott.

Dr. Robertson: Yeah, and that's why, to me, it's when you make the next major, you know, big change to how the Plan is set up is -- if you put it around a lifespan thing, you won't be like, "Well, I missed this spot. I missed this spot."

Well, you just make the assumption that we're just going to be talking, you know, across the lifespan, that we're not going to just pigeonhole it into you know -- and that way, you don't miss adolescents. You don't miss adults. You're just covering, and you're just assuming that we're going to want great supports and services all the way through that go with individuals and that change -- as challenges change, you adapt to that. What happens with puberty, what happens in employment as someone -- you know, as they get older, things are going to shift in the difficulties.

There's just a couple of brief comments

to that. One of which is, and just to mention kind of in passing, and it should be out I think maybe in the next year or something -- there is still some kind of testing that's happening with it -- is that in the adult area as a resource. And I think we -- you know, if there's more funding out there, more could be done like this, is that the folks out in Oregon had also developed through NIMH funding, I'm happy to say, like a toolkit for autistic adults to interact with health care service providers.

That's unique. That was kind of a creative idea looking at the challenges that can happen with the patient-provider communication with autistic adults going into health care settings. That was provided by inputs from some other research saying that's a problem. We need to address that. And that's an example where the community provided input, and we got something kind of that's really meaningful and that very likely with testing will bear it out that toolkit is

going to be helpful for folks.

And maybe if you could have more research like that that's kind of like part and parcel community-based participatory research, but part and parcel something meaningful that's like a product that's produced that kind of where it probably doesn't necessarily even cost that much to do, but it can actually have a big gain, and you can be collecting data on how it's working and be developing a product that's useful for a lot of people at the same time.

But the other comment that I wanted to mention related to kind of these shifts in terms of across the age span, why can't we also be looking at -- and I'm kind of surprised that I've never seen it in the research in here or other parts of the Plan is for individuals, as they've gotten older -- to be looking at like, for instance, that -- and I don't really -- I'll be honest. I don't really like the categorization that was used in that study of optimal outcome or

whatever characterization is.

I like to think of it as more adaptive, you know, have the right supports and services to get through adversity. With a study like that, it's more on the superficial level that it kind of says this group of individuals versus this other group of individuals.

Well, can you dive in deeper -- and why aren't we doing this in the Plan right now in the last several years is -- diving deeper on what supports and services were meaning that enabled naturally or otherwise these individuals to be achieving better than the other individuals? Were they "supposed to be like that" when they were kids or was, you know, more likely -- or were there things that happened along the way that separated that group out from others as far as supports and services that they were able to access?

And so why can't we be doing that and studying, you know, adults that have been able to get through certain challenges and

saying, well, what happened there? What happened to your family relations? What happened in adolescence? What happened as you got older? What was meaningful? What was not working well?

Tease that out. Tease that out also for adolescents, for instance, that are doing real well and saying how can we be benefiting other individuals that are struggling and saying, you know, what support services, what ways in terms of strategies were those individuals learning to use? They were taught by their families. They were taught by school.

We don't do a good job of that at all, looking at individuals that, as I say, have adapted and saying what can we learn from them? What can we learn for adults and adolescents?

I mean, I never -- I never really see that in science, and I don't really see that here in the Plan, and I'm seeing some nods a little bit on that is that is -- could be

something fruitful, I think, for the future is learning from individuals, learning from autistic teens and adult successes and using that to help other individuals who are having more challenges.

Dr. Insel: Thank you.

Other hands up here? Let's go back to Jeremy, and then we'll finish up here in a couple of minutes.

Dr. Veenstra-Vanderweele: So I think we talked earlier about the frustrations with timescale with clinical trials. This is almost the opposite problem, where if you look in topic area three, there's really a dearth of research using longitudinal study designs, and this is where the 5-year window with funding is really challenging.

You, generally speaking, don't get through review if you propose a longitudinal study that's starting. You have to have something else in the first 5 years, and then, oh, now I've got it longitudinally 5 years later. It's really hard, I think, to

set up some of these things under the current funding mechanisms to follow some of these questions.

There is very little done on puberty, sexual development, some of these things that are straightforward questions, but you have to start before and follow through. And we're just not really well funded, or our funding system isn't set up for that as much as for a lot of the other questions we ask.

Dr. Koroshetz: Well, I don't know about Tom's Institute, but this comes up to us quite a bit. And it's true, except looking at our portfolio, we have studies that have been going on for 20 years. So they've been getting renewed every 5 years for 4 or 5, 10 times.

So it is doable. You do have to show progress each time, but I think everybody realizes, and actually it becomes more valuable as time goes on. It's actually hard to shut these things down, but they are certainly important, and you can't do without

them.

I'm also struck that besides for the randomized controlled trial, there's a lot of people now are trying to think about ways to getting information from prospective databases because now, you know, they're looking at big data that comes in through other ways, like electronic health records or things like that.

So there may be a new science coming forward that allows us to do that if you have collected the right data. The technique that I'm most familiar with is something called propensity analysis, where what you do in a randomized controlled trial is you separate people, one group A, one group B. And what you're making sure of is all the confounders that would influence outcome or treatment are basically balanced just by the fact you flipped a coin.

But you, theoretically, can figure that out prospectively what are the things that would affect whether a certain person got a

treatment or not and identify two people in a prospective database that are otherwise alike except they got a different treatment and then look to see what the outcomes are.

But certainly, that works -- you know, it's going to be harder when you have to wait 5 or 10 years to get your outcome. But it may be the future to answer a lot of these questions.

Dr. Insel: So before we close this down, let me just again make sure that for David's purposes, since David has to write this up, if the question is what have we learned over the last 4 or 5 years on what does the future hold, have we captured that here? Is there anything else that you'd want to make sure David includes in terms of progress?

Stan, was that your comment or --

Dr. Niu: Yes, I just want to make a couple of comments. I heard here that, you know, the future is very broad, and you know, it can be many areas. I just want to make a couple of comments on the small progress, you

know, we're making in pipelines.

One area we have funded a project. We talk about life skills. One of the projects we're funding trying to teach those young adolescent to learning the driving skill. We talk about skills in the transition to independence. This is one small step, but it's an important step so we can help them to gain the skills.

And also we have some trials -- one of Nancy's trials I believe is also the adult population -- teaching them the CET intervention, help them to improve, continuously improve the cognitive skills. I mean, social realms. And so I think there are some small progress on the way.

Dr. Insel: Right. So if it's possible, I think for this purpose, for the purpose of this report that we're going to put out, we won't be able to say we've funded it. We're going to have to be able to say we've funded it, and this is what we got as a result. It has to be -- we have to be able to say that

in 2008, this is what we knew, and in 2013, because of the investment, we know X, Y, and Z, which was not clear before.

So what David's task here, with your help, is going to be, to try to capture what is really new information, if it does exist. And if it doesn't and if it's just in process, we can say that, but it's more of a promissory note then. And I think for this report to be most effective as an Update, it will be great to be able to talk about the things that have actually been completed and are really entirely new.

Nancy?

Dr. Minshew: I think that what I would add is that there is enough evidence that things are getting better, that outcome is improving. Whether you look at some of the earlier or intervention programs that they're doing and they're having a harder time demonstrating that the new intervention is better than the community intervention because the community interventions have

gotten so good, or we see reports that there is a good outcome, that some of these children are outgrowing their diagnosis, so to speak, at various ages, whether it's childhood, but more adolescent.

And certainly, the studies that we've done, they're adults. Now these are verbal adults to start with, but still significantly disabled. They can improve substantially. And processing speed improves; they acquire a perspective-taking capacity, a capacity to be "gistful."

The other thing is you see this correlating or corresponding changes in brain systems, and it becomes self-propagating. So that a year after the end of the treatment they are better than they were at the end of treatment, and we're expecting that at 2 years out, they'll be even better.

And then, finally, that the study that reported that having a job, being in a job resulted in documented improvements in executive function and memory. So I think

we've learned a lot, and the last thing I'd say to parents who have, say, very low-functioning kids is that there's enough work that's been done defining molecular pathways that I would think that within 20 years, we'll be able to change the brain with biologic systems.

And we didn't -- you know, with biologic interventions -- we didn't -- we weren't able to say that before with much confidence, but I think we have proof of concept already, and it's a matter of time. So what's going to happen to the adults? Well, they're already getting better. We can't -- we know some of the things we have to do, and then the biologics are going to come along.

Dr. Insel: Other input for David? Any other comments, thoughts? Yeah, well, Amy had her hand up, and then, Jim, we'll give you the last word.

Dr. Wetherby: So what strikes me is, number one, the commonality across the lifespan, the needs. And then when we think

about the limited research funding that we've put into adults, but yet the greatest service cost falls to adulthood, and there's no accountability across these systems.

And so, we miss the children on early intervention. The school system doesn't do a good job, but they graduate the students anyway. They go to become adults and can be, you know, very -- and I don't mean to be the downside of what you're saying the upside. There is an upside to that as well.

Catch the children early. We provide early intervention. Those children maybe make it in general education. The school systems saves the money, but it costs the eye. Then those children maybe graduate. They get to college, and then they kind of fall off a cliff because there's no support at college, but they have potential.

So I think the division of systems between health and education and adult care -- wherever that falls -- I think you play a role in that -- is really broken. And I would

like to see NIH take a leadership role, or HHS, in coming up with a research agenda and partnering with the U.S. Department of Education. And I think Medicaid, in a sense, has probably the most to gain from the cost in adulthood if we could all do better.

So, and I think Paul and David are really the people that have this incredible expertise to guide this.

Dr. Insel: You know, Paul and David, every time we talk about you, we look skyward.

[Laughter]

Dr. Mandell: Well, we're both very tall. And Paul had to leave.

Dr. Insel: Okay. I'm going to let Jim make a final comment, and then David, we'll send it back to you before we break.

Dr. Mandell: Okay.

Dr. Perrin: Yeah, just two quick things. One is I don't want to consider adolescence a black hole. These are tremendously exciting young people and so many young people with

autism who are really kind of neat, especially as adolescents. But we have a lot to learn there.

And I guess the broader issue is, you know, we know there's a huge diversity in the population of young people whom we work with and study with autism spectrum disorders. The same thing is true for adults. There are many adults who are doing incredibly well. I mean, any way we talk about it. They're very functional, very productive, active adults.

And we need to understand that there is this breadth of functioning both in little people and in big people. And understanding the progress toward each of those would help us a lot designing better programs. We know more about that diversity than we did 5 years ago.

Dr. Insel: Good. Yeah, David?

Dr. Cheak-Zamora: This is Nancy Cheak-Zamora.

Dr. Insel: Go ahead.

Dr. Cheak-Zamora: Sorry, my phone wasn't

working earlier. I did want to just point out, reiterate that transition is really important. So we haven't been funding that. That was partially in Question 5 and in Question 6, and we haven't been putting a ton of money into it. So I think that's an area where we can improve on.

And getting the perspective of adolescents and young adults, too, in that process I think is very important and can help us to tailor our interventions to meet what their needs are. We've been talking about that sort of continuously, but we don't actually ask them very often.

And then really push future -- various agencies that are collecting the data to not just stop at 18. So in terms of these survey mechanisms, like the ATN and the National Survey of Children's Special Healthcare Needs; they stop at 18. So then our data stops, and such great data up until that point, but then we don't have anything to lead us further.

And finally, I would say scalability is so important. So we do have a lot of studies going on about life skills, about health care transition, but they're small, and they are in very minute -- they're in small populations within all of our sort of practices. And so we have to figure out how to make those large scale and actually put the information and disseminate it out there.

Dr. Insel: Thank you. David, last word?

Dr. Mandell: Well, I was just going to say that I've already been emailing with Paul, and I'm hopeful that he and I are going to get together to do the update for Chapter 6 together.

Dr. Insel: Perfect. All right. Great discussion. Gosh, a lot of interesting ideas, and you know, I understand the tremendous needs, but there are also some elements of hope here, which is kind of great to hear.

Let's take a break and reconvene at 3:30 p.m., and we'll finish this up with Question 7 and then some final thoughts from all of

you. Thanks.

(Break)

Dr. Insel: Okay, it’s back to work. If I can have you take your seats. We’ve got one final pitch to towards the summit here, and then we're done. So we're going to go to Question 7. And this one is really different than the first six, right, because this is one where we should be able to get pretty quantitative about what we had and now what -- in 2008 -- what we have now: "What other infrastructure and surveillance needs must be met?"

I'm going to turn this over to Alison Singer, who will take us through.

Ms. Singer: Nothing like doing infrastructure last. Okay.

[Laughter]

Ms. Singer: So the one thing I want to just point out is that Question 7 was only added to the Plan in 2010. So we're really at this point only looking at progress over the last 3 years, as opposed to the other

questions, which were 5 years.

So the aspirational goal here is "to develop and support infrastructure and surveillance systems that advance the speed, efficacy, and dissemination of autism research."

And one thing we talked about in this -- in our Group was -- that the way the Plan was written -- it was really designed to highlight gaps. And funding for infrastructure is something that's ongoing and requires continuous investment. So that there was a lot of investment in infrastructure that couldn't really be captured in any of the objectives, which were designed to look at gaps.

So in this particular chapter, more than 25 percent of the funding is in “Other. And “Other” may not be the right name for what is included in “Other. It really is core infrastructure that is in -- is captured by “Other.” So I just wanted to start there.

Also we had some difficulty in terms of

how we applied funding to some of the objectives. For example, one of the objectives called for supplements to the ADDM Network, but we weren't able to really tease out what money was for supplements versus what money was for the ADDM Network overall. So it looks from the report that $23 million was for supplements to the ADDM Network when, in fact, that was the overall Network.

But the 2012 Plan included 16 objectives in Chapter 7, and our Group felt that in 8 we had made substantial progress. We felt that the autism community now has a well-organized database to track work that's funded by the Federal Government and private foundations, which was something that was not even included as an objective but is an incredibly valuable resource that was developed in the process of evaluating -- doing the evaluation for this Committee -- which is a resource that is not really available for any other disease, but it provides us with a lot of great information. And that was done by Susan

and the group at OARC.

We also have new and appropriate tools that scientists can use to communicate their findings with stakeholders, not necessarily Web-based tools, as are in the specific Plan, but we thought that they did have tools. So we could actually -- I don't know if we want to go through each of these, but we found that in many cases, in eight of the cases, there was good progress that was made, not necessarily specifically what was written in the objective, but that really met the spirit of the objective. Or in some cases, it had been accomplished not through Government funding or autism funding but by funding that came from other organizations.

So we thought we had in general made good progress here. There were a couple of objectives, four specifically, that we felt really were no longer necessary or had been completed. And we also wanted to just make sure that as we go forward, we realize that even though there were certain projects that

we felt we had accomplished -- like we had, for example, created programs to enhance the workforce. We wanted to make sure that even though those had green lights and were considered accomplished, that we realized that in infrastructure these things require sort of long-term care and feeding and long-term maintenance and that continued funding was necessary to maintain the infrastructure inroads that we've made.

So in terms of what has improved, before I sort of hand it off to the other members of the Committee, a couple of things that we noted that had improved were awareness, and we can measure awareness. I disagree with you. I think we can measure awareness. We can look at base levels at different years and levels of awareness through the Learn the Signs campaign and through the Autism Speaks ad campaign.

Dr. Insel: That's great, but do we have numbers? Because I think --

Ms. Singer: We can get numbers.

Dr. Insel: Yeah, we'd love to put something like that in the report. That would be really helpful for an update.

Ms. Singer: So we have databases like NDAR. I think Dan reported that 90 percent of studies were now filed through NDAR. He can talk about that more in just a second.

The IAN database has been really a model for using -- for doing rapid studies of questions that come up in the field. A good example is the wandering study. If we did not have the IAN database up and ready to go, there is no way we could have quantified the level of wandering in the short amount of time that we did.

I think from start to finish, that study was 6 months from the time we sat at the table and said we should do this to the time we had data to present.

And I think that we talked about the fact that we need more organized systems to encourage families to participate in research and to join registries, that that had

improved. That more families were participating in research, but that was also -- while it was an area of improvement, it was also an area of continued need when you looked at the number of families in other disease groups who are participating in research and in registries.

So that's a short summary. Maybe I'll hand it off to others in our Planning Group like Paul, who's sitting next to me.

Here, the mike's already on.

Dr. Law: This is Paul. I should say that I'm actually in the process of leaving Kennedy Krieger. So I shouldn't have that underneath my name there at the moment, but it will be a very nice, smooth transition. So don't worry. IAN is in good hands.

We only had about 3 months from the time you asked us to do the wandering study until it was completed and reported to IACC, as I remember the months. But --

[Laughter]

Dr. Law: But --

Ms. Singer: It always feels twice as long to the families as it does to the scientists.

Dr. Law: But yes, my general comment is that in addition to that study, one that's not been publicized quite yet is we were able to do a randomized controlled trial involving like maybe 40 States or something like that, an online clinical trial, and accomplished that in about 10 weeks from beginning to end on omega-3 fatty acids.

And as we were talking earlier about the importance of looking for new ways to do experimental research quickly, I think there's a lot of creative ways we can think about doing that. I think any intervention that's reasonably safe, which I assume this cardiac example was, Tom, that you mentioned, there are ways of trying to do that pretty quickly using large social networks like IAN.

And that includes technology interventions also, and I think that's important not just because it answers

important questions but also because it gives the sense to the community that we're being very responsive and affords us some forgiveness for the slower progress that is made in some other types of research just because of the nature of the type of research that it is.

Dr. Insel: Other people from Question 7? Dan, were you part of that?

Mr. Hall: Sure. You know, I think the objective on a lot of the initiatives related to the technical infrastructure was to establish, you know, establish IAN, connect up these various databases, and we're there. I mean, we have AGRE, IAN, all the NIH data in NDAR, and soon we hope we'll connect up to Simons. And we're putting in the terms and conditions, so the data is coming in.

We do have now -- you know, 5 years ago, we had no data shared effectively, you know, some in research systems. But now we're up to 80,000 research subjects shared. That will be over 100,000 by this time next year, we

estimate. We have 7,000 exomes, as I mentioned before, available for computation. This data is up in the cloud, so to speak, and is -- you know, scientists are now computing against that, launching thousands of computers against this data to look for biomarkers and really unleashing the computer to do that.

So these things are happening, and they are reaching these aspirational goals. But, and are we satisfied? I don't think we are. I think there is so much -- as Paul pointed out -- there is so much untapped potential by bringing in the parent populations to, you know, provide geolocation where we can overlay environmental data onto the 7,000 exomes that we have -- you know, capture more and get the message out there.

We can -- we can grab all this broad data and crowd source, so to speak, and provide the researchers the power much more than can be done in any one lab. So I think it's really now tapping into this potential.

Dr. Insel: Anyone else? Cathy, were you on this Group as well? Go ahead.

Dr. Rice: It seems like I was on every group. I think just to capture the changes in the last several years in surveillance is having the infrastructure, particularly of the ADDM Network, to build upon of not only having single year of estimates but within the same sites having multiple years, where we can look beyond prevalence and look at some of the characteristics of the population that's changing over time.

But that also during this period, that that has served as a base onto which other questions can be added. So some States have done additional data linkages, like looking at medication use or participation in juvenile justice system, to really understand more of the needs of the community related to that population-based cohort. It's also provided the opportunity for other organizations to offer supplemental funding like Autism Speaks has with one site who's

doing complementary direct screening to supplement the records review methodology.

There are many other ways that we could expand. We've added on younger ages, but the opportunity is there to follow up cohorts into adulthood, to do additional data linkages, to do specific hypothesis-driven analyses. But we have that infrastructure there that's just begun to be tapped.

Dr. Insel: Anyone else on Question 7? Any other comments?

(No response)

Dr. Insel: All right. So let's open this up to the whole group. Other questions or comments about it? Yes, go ahead.

Dr. Durkin: Hi. It's Maureen. Hello? Can you hear me? It's Maureen Durkin.

Dr. Insel: Yes, go ahead.

Dr. Durkin: And I'm on the -- I was an outside person for this Group 7, and I just wanted to point out a couple of things related to surveillance. One of them is just in terms of accomplishment, I think we've --

the country has -- accomplished a lot on this goal in the sense of improving the, you know, the surveillance reports and improving our information on just the number of the children with autism across the country. I think that's a huge accomplishment.

I think it's likely that we're going to be finding numbers not unlike what was reported from South Korea in more and more locations around the country, which is well over 2 percent of children on the spectrum. So that then we have to ask the question about functioning, and right now our surveillance system isn't able to provide any information on this. So we don't really know much, and that's a neat criteria for autism disorder.

So I think in terms of future research, this is something that's needed -- is in the surveillance realm -- is a way of monitoring functional status in addition to just other criteria are met, as well as monitoring quality of life and all those other things

that have been talked about today.

I wanted to also mention that one of the things we've been able to learn from the surveillance data is that we can track the age of identification, the age at first diagnosis over time, and this is one thing where we've not seen any improvement since the ADDM Network started. But it holds out that -- it relates to the question of Group 1 earlier this morning when we were talking about what is the earliest age of identification and what's the sensitivity and specificity predictive value of the tools?

One of the things we've learned from the ADDM Network is that as the -- as the prevalence increases in the population, we're identifying a greater proportion of children with autism who are having normal IQ and are having -- I don't like to use the high-functioning autism, because I'm not sure what that means -- but they're meeting diagnostic criteria with fewer number of symptoms, and this is something that we've published on

from the ADDM Network.

And what it means is that as we identify more children with -- one of the biggest predictors of an early age identification is cognitive impairment. So children without intellectual disability are identified later. As we identify more children with autism with normal intelligence, we're getting a later age of identification.

I think the reason this is important is we are making progress in the sense that we're identifying more children, but we're not going to bring the age of identification down that way because we're identifying more kids whose impairments -- are in the realm of -- impairments appear in their actions and things like that aren't apparent early or until later.

Now maybe it is possible to identify these kids at age 12 months, but I'm not so sure, and I don't know that we've shown that yet. So I think these are some of the things we talked about in this Group 7 I just wanted

to bring up. Thank you.

Dr. Insel: Okay. We'll start over here. Karen?

Dr. Pierce: Yeah, just one comment. I think you're probably referring to the CDC study, the ADDM study that came out, and that was published in 2012. But if I remember correctly, it was based on children that were 8 years old in like 2008 or thereabouts.

So really you're looking at kids who were born in the year 2000. And so, I think if you really -- we really had data on kids that were born in 2011, 2012, you know, in Amy's work, my work, Deborah's work, everyone was really going in earnest, if I could get the true number, I think the mean would be lower nationally. It wouldn't be 4 or 5.

I don't know how much lower it would, but I'm saying it's a little bit of an artificially negative estimate because you're looking at data from kids, you know, 10 years ago.

Dr. Lehner: Thomas, just to address

another infrastructure point is the issue of biorepositories. We have greatly expanded the number of samples in a major biorepository to more than 27,000 samples, of which 16,000 are in the current distribution.

So when I say samples, these are many of these are either pedigrees, trios, or multiplex pedigrees. So there are about 6,200 cases in the current distribution. So it's a rich resource for doing genetic and related studies. The samples have an intensive -- many of them intensive -- phenotypic and genotypic information already.

We've also recently expanded collecting fibroblast lines and iPS lines. We have, I think, 20-plus fibroblast lines and 25 iPSC lines.

Dr. Insel: Do we have numbers for 2008 so we could make this a delta from where we were?

Dr. Lehner: We can make it a delta. I think that it's about -- it is twice or two and a half times as many.

Dr. Insel: In terms of the DNA, and I assume that fibroblasts were zero?

Dr. Lehner: That was zero, yes. And iPSC, too.

Dr. Insel: And then the -- so I think this is great because what the report should have, and maybe it should even be in a table, is to document exactly what's in the national bank for all kinds of tissues and other kinds of resources that people might want to do research on.

What about brains? Do we have a number for the number of brains of people who died with an autism diagnosis?

Dr. Lehner: So we don't have an autism brain collection. Autism Speaks has, and I believe there are about -- the gentleman can tell you that -- about 40 brains in the Autism Speaks brain bank?

Dr. Insel: And Alison may know more about this.

Ms. Singer: So I don't have the exact number. David could probably give us the

exact number, David Amaral. But I know that this is one area where we've actually regressed, where we now have fewer brains than we did when we started the Plan in 2008 because of the freezer malfunction and the tremendous loss of resource there.

So this is not really a -- I mean, this is extremely sad that we lost those resources.

Dr. Insel: Yeah, at the same that it's become clear that the brain is so different than anything else that you want to measure. So without the tissue, there are major questions from 2, 3, and 4 that we're probably not going to be able to answer.

So I think in this reporting out as you put it together, I'd love to actually see numbers, if we can. I think the public should see that. And if we've gone down in an area that's so critical, it does highlight the need to do something very different.

I know you're involved, and NIH has just announced a national neurobio bank effort,

and there will be a bunch of things happening as a result. But we do need to feature this.

Carlos?

Dr. Pardo: Just a brief comment about brain bank. It is not only the brains from patients with developmental disorders and autism, but also controls. There is an urgent need to accumulate a very good number of controls because there is no way to collect data from diseased brain if we don't have controls.

Dr. Insel: This whole area is so difficult for everybody. And in terms of what the IACC can do, if we can create a consortium here where the nonprofits or the advocates with families are working, maybe doing a campaign -- I know you're planning to do this, Alison -- to educate the public about the need.

And we can provide the funding for actually getting the bank set up and a registry, as we're doing, so that everybody anywhere will know what's in the bank. And

standardize the collection and the way that the tissue is processed and have some fair way of distributing it. We can really change this all. This is all doable. But it's a great place for us to coordinate.

So if you're on the phone, please remember to mute unless you have something you want us to hear.

Scott?

Dr. Robertson: So just a shorter comment before a longer comment. My shorter comment: I wish folks would at times -- I mean, I know there's a lot of scientists in the room, but -- and I know you use these kind of terms you float around sometimes in research, but I would be kind of careful at times about the language you float around saying, well, with "normal intelligence" means you don't have intellectual disability.

I mean, sometimes we say things that kind of are really -- you know, if I had someone -- if I had a colleague or friend with an intellectual disability in the room,

they would not really be happy with the way that was construed, that it's kind of not normal to have an intellectual disability. Why can't we just say without intellectual disability, you know, instead and be more respectful in terms of our language?

But the broader comment that I wanted to make related to what's in here on one of the objectives. It specifically says in here expand the number of ADDM sites in order to conduct ASD surveillance in children and adults. Yet this, we're not having that in terms of data collection around adults related to surveillance in here.

It says it looks like the farthest that went up to was 15, 18, which is still -- basically, that's still the adolescent population. And I don't -- can someone elucidate, maybe educate me on the barriers and why that's not able to happen?

I don't want to put anybody too much on the spot. When I was at a previous public health conference recently, the American

Public Health Association conference, I was asking folks from the CDC why can't we have -- you know -- do surveillance around adults? And the response I got at the time was that's too expensive.

We can't do it. It costs too much. It's not going to happen. And it wasn't exactly the answer that I wanted to hear, especially since I hadn't realized -- at the time, I hadn't seen the exact language on that, but it is actually sitting right here in the objective that we're supposed to be even expanding toward adult.

So can someone help me understand the barriers that are happening on why we can't be expanding the ADDM sites, as proposed on here, to be finding out what it looks like as far as even just basic population numbers among autistic adults going up through the age ranges?

And then, as some of the other things that we're talking about, expanding beyond just basic population-level numbers in terms

of some of the other things that are happening, like connection to, like, the justice system and things like that. We could be doing that for adults as well.

So can -- I just would like to know why we're not doing it. What's -- you know, what's the reasons for it not happening? How could it be kind of improved in the future to go in this direction? So this is really important to be gathering the same kind of data we're getting across the board for children among adults, including among prevalence for different age ranges.

Dr. Insel: Cathy?

Dr. Rice: So Scott, that's a great question, and I don't know who responded to you from the CDC, but it shouldn't have been a blanket it's too expensive to not do that. It may have been framing -- basically saying in flusher times -- when we actually had a little bit more funding, we did put out an RFA to get proposals about how people could approach adult surveillance.

It's a lot more complicated than -- I mean, children's surveillance is hard enough. It seems pretty easy to count. Why can't you count the kids faster and find them? And the challenge we've had is that, you know, we do not have an integrated service system and a way that we can access everybody. And that's even more so the case in adults.

Unfortunately, when we put out that RFA, we really didn't get any good applications. And since that time, I can't say that we've had the funds to follow up on that, but there certainly has been interest in doing that. But we do have to recognize the challenges in adult surveillance in that, you know, there's not one place like a school system where the majority of adults can be accessed.

We have the challenges of institutionalization, for instance, of homelessness, of incarceration, of all the places where somebody could actually be residing. And so some of the efforts of following up on known cohorts like in Utah

have been successful, and I know there are other small efforts of looking within particular populations, like, I think David Mandell is doing a study in psychiatric populations.

But within the U.S., we really need to think about what the purpose would be for us to do adult surveillance, and if it's just to get the number, that's going to be more challenging to do in the U.S. than it might be in other countries. If it is to understand needs and outcome and functioning, we do have some opportunities with some of these established cohorts that could be followed up upon, that we knew and identified them when they were children and adolescents and followed them later on. Maybe some opportunities for getting more of that functional information, and hopefully, that remains an objective, and when funding is available would be something that we could look into.

I don't know if you have anything to

add, Coleen?

Dr. Boyle: No. I think that was terrific, but -- and I would just emphasize Cathy's point about the fact that we've been following children now who were 8 years old. And it was pointed out earlier that we've been doing this for quite some time. So those children are young adults or even middle age in their 20s -- I wouldn't say middle-aged adults, but in their midtwenties. But so we could, you know, with opportunity and resources, be able to look at that issue, at least start to look at that issue.

Dr. Insel: Other comments? Idil?

Ms. Abdull: So I wasn't in this Group, and I wonder if I could just ask a question in terms of the ADDM system that we have now, which the last funding actually decreased. So less States have the ADDM system. So we're going down, not up.

And also the 1 in 88, it's kind of -- Utah has higher number. Alabama has lower number. So do we know why some States are

higher than the others, number one?

And number two, are we doing any infrastructure to figure out in terms of diverse communities? So are African Americans, Hispanic Americans, are they getting -- in the ADDM system, do you know what the ethnicity is? And then also does it matter the urban versus the rural, if that would make sense?

Dr. Julie Daniels: Yeah, I mean, I think that what we've seen over the decade that we've been doing the surveillance with ADDM is that the disparity between black children and white children was much greater in the early years that we were doing the surveillance than it is now, where it's fairly equal. The Hispanic community is still, I think, underdiagnosed. That's the target that we're looking for at that same level. And so that's to answer that question.

And then what we've done in North Carolina with the ADDM data is looked at urban/rural because we're one of few States

that have both urban and rural areas under surveillance. And what we've noticed is that in the early days of our surveillance, we had real paucity of autism diagnoses in rural areas, and where we saw the pockets of higher prevalence was really around the university centers and things where we were really early adapters of screening and uptake of those diagnoses.

In recent years, what we're seeing now is that there's pretty much a flat prevalence across our region, which I'm liking to interpret in an optimistic way that what's happening is that the rural areas are catching up in their rate of diagnosing the children who should appropriately be diagnosed. We're not seeing an increase at that same rate in the high-prevalence regions that we were previously diagnosing. We're seeing the catchup in the rural areas.

Now that's just one State, but I think it, to me, sends an optimistic message that we are trying to reach out and catch up.

Ms. Abdull: So do we know why Utah is high -- maybe Cathy or Dr. Boyle -- and Alabama so low? I mean, is it because they're just not being caught, or is there something in Utah that's making these kids get more autism?

Dr. Rice: Yeah, that's a key important question, Idil, that I wish I could say, yes, we know the answer to it, but I think it's very tied to what causes autism and what is causing the most of autism. We know a lot more about the sites that have lower prevalence. We know the gaps in their data as to why they couldn't find as many kids.

But those sites that have higher prevalence, like New Jersey and Utah that's approaching in similar to the South Korea study, you know, our best estimate right now is that that is better ascertainment and better documentation of sites, and we're still in the midst of a changing situation as we collect data.

As you know, every few years, we revise

the estimates based on the best information we have at the time, and the information we can get keeps getting better and better. And I don't think we've yet flattened out like Julie just mentioned in North Carolina, that we are seeing some equalization in urban and rural in some areas, across race and ethnicity in some areas, but we're not completely flattened out geographically and in all of the different areas.

And I think until we -- if that is a reasonable thing to expect, if the assumption that autism truly, given if you did not have variation and risk factors, would be equal across the areas -- until we have a period of stable prevalence, it's going to be hard to really use those data to evaluate things like environmental risk factors.

Dr. Insel: Alison, are you okay on the surveillance side? Do you feel like there is something we need to do to help you with this report related to the infrastructure for surveillance?

Ms. Singer: No, because at least Cathy helps with this.

[Laughter]

Dr. Insel: So she's going to do it. Okay, because it does sound like there have been real changes over the last 5 years, and I want to make sure we capture them the right way.

Dr. Julie Daniels: Yeah, and I guess just to sort of put an exclamation point on it, I think that this discussion couldn't have happened to the same level 5 years ago because we didn't have multiple data points on a timeline that would allow us to even ask these questions.

Dr. Insel: At the same time, so we have the South Korea data, which has come in over the last 5 years, and we also have this comment that people have made that we really need something that's in real time as well and the need to actually capture something far more recent.

There were hands up over here. Joe?

Dr. Buxbaum: So two comments about repositories. The first is I think it is amazing the number of samples that have been increased in our major repositories and other repositories. I also think it's amazing that so many have been run through all exome sequencing. We're almost on par with GWASs in terms of number of samples, and we may surpass it pretty quickly.

And so I think we're doing pretty well as the glass half full. The flip side is that compared to other complex disorders with similar kind of loading, we have much smaller samples available to us, and there's very good empirical data that will tell us that if we could double our sample size, we will probably double the number of things we can discover.

Obviously, as more ascertainment goes forward, layering environmental data and the kind of birth data and maternal data will be very important. So we can make a more robust data set going forward that's useful for gene

by environment and gene-environment studies.

Another thing about the brain banks, I think it is a tragedy what's happened. Obviously, NIH is getting behind kind of a federated brain bank system, and it sounds like you're willing to take a more muscular approach here.

I think one of the difficulties with the brain banks to date were that, you know, there are certain obvious things that you almost want to do with any sample. You want to do genotyping. You want to do RNA-seq, obviously, sorting. But you know, a lot of those studies became the private domain of individual investigators, and the tissue is just too valuable and the baseline experiments so straightforward, I think, to identify that I think when you think about brain collections. I think there are a certain number of things that everybody agrees should be done on the sample and be made available immediately.

I will say also that it sounds like the

U.K. is doing very well on brain collection, right? They seem to have an equal sample size as compared to the U.S. in just a few short years. So they're doing something right.

Dr. Insel: That comment reminds me to ask, it wasn't clear, Dan, when you described NDAR. Does NDAR have images as well from all? Because we talked earlier about all the imaging experiments, and we've done really well now to put all the DNA into a public access repository so people can use it even from anywhere.

What about the imaging? Do we do that in the same way?

Mr. Hall: So yeah, in NDAR now we have, I think, images on over 2,000 subjects. So, and you know, this just keeps building upon itself. Because as you're going through and doing these sequences and you're getting the results from those sequences from many different computational approaches, so you can start comparing the OMIC alterations that are coming in on those sequences, as well as

volumetric data from imaging, and now you're able to look at these things as almost endophenotypes just like severely affected, affected, IQ, executive functioning.

So this is where we're going, and as we keep layering this data up, it holds a lot of promise. I mean, I'm a computer scientist. But we just keep adding more data on top of existing raw data, and that's going to help.

Dr. Insel: Is anybody looking at it?

Mr. Hall: Yeah, we have a -- we have a number of labs that are doing this. So we're not doing this base-level alterations or doing volumetric analysis, but labs are doing that. And what we ask is get the results back to us.

So when these results happen, we want to see what those results are at the subject level so it allows others to look at the correlations based upon those results. So yes.

Dr. Buxbaum: Can I ask a follow-on question? So I think Walter mentioned before

this large resting-state study with 1,000 samples -- 500 kids and 500 controls through the ABIDE consortium. And I think -- I don't think ABIDE is in NDAR right now, but I suspect that NDAR has a lot of data on the ABIDE participants that could be linked, and it would be fairly significant.

Mr. Hall: Correct, and we are working with Mike Milham in bringing that data in. So any of these repositories or existing data sets we'll gladly accept and make that available, and then we can see the overlap.

Because, you know, for instance, in a lot of the data, we're getting the sequences in, and then there's microarray done 4 years ago. And so we're starting to see this layering kind of capability, and you know, we don't do the analysis, but we're putting it out there. And one of the points I wanted to get across in this meeting is these kinds of things are able to be done now, and it could dramatically accelerate scientific discovery, which is our goal.

Dr. Insel: Yeah, no, I think these are enabling in so many ways. What would be helpful again for Alison and for the report is if we have examples of someone -- and could be from Bangalore or Beijing or Boston or wherever -- who hasn't actually collected the data but can go into a registry or a repository and make a discovery or test out an idea or advance the science quickly because of that, that would be just great to be able to cite.

Mr. Hall: Yeah.

Dr. Insel: That's the -- I mean, that is the purpose of all this -- is not just to collect it but to actually have someone use it and find something.

Mr. Hall: Sure. Yeah, there was an article in *Cell* last week on just that. I mean, we don't have as many papers out there as we would hope. But we are seeing a lot of -- in grant applications that using secondary analysis as an aim are coming in, and it's encouraging for us.

But we're not really happy with the -- with where we're at, but you know, our user base went from a year ago 50 to, you know, near 300 users in 10 countries. So I think we're working it out.

Dr. Insel: I'd put that in the table as well. I mean, I think we need that. We need numbers for this --

Mr. Hall: Sure.

Dr. Insel: -- that are truly an accounting. This is an Update that's going to be based entirely on numbers. So the extent to which we can get that granular, the better we'll be.

Mr. Hall: Our Web site is out there, and you can, without requesting access, really see the data that's available for research. So we encourage the scientists to go look.

Dr. Insel: That's great. Okay.

Dr. Durkin: I'd like to a build little bit on those comments of Joe and the computer scientist in terms of various layers of domains, dimensions, what have you, and what

Joe was saying in terms of the issues of deep gene sequencing and adding on phenotypic and environmental data.

There has been a project funded through Autism Speaks to develop a fairly brief environmental and -- an environmental and nutritional questionnaire -- that could be -- that is being developed to be made accessible. I think one of the best uses of this instrument is called the ELEAT instrument. I've forgotten the acronym, Early Life Exposures Assessment something.

And I think one of the big, major uses where this could be very -- really help advance some of the gene environment interactions is for many of these large gene databases to go back and get some of this environmental and nutritional data, particularly focused on the prenatal period.

That can be difficult. That's challenging to get data retrospectively. But given how large some of those databases are, even a limited analysis to, you know,

children born in the last 5 years might well be enough to really advance that science.

I think the existing databases such as there are that you can link from address data can provide us with a lot of information, particularly around air pollution and air pollution-related sorts of variables. But air pollution is a pretty limited set of exposures in the life an individual where probably the number of chemicals that were introduced through household products or through personal care products like the shampoos and the lotions and scented air fresheners and so forth and plastics and so forth in our prepackaging kind of outweighs, I think, by probably several orders of magnitude what we can get from the existing databases.

So these are the sorts of things that this instrument has been designed to try to capture. So it's a resource I think that going forward would be very beneficial for, again, integrating environmental and genetic

data and on the etiologic side. Thank you.

Dr. Insel: Okay. Other comments? Matt?

Dr. Carey: I was going to go back to the topic that Scott brought up of adult prevalence. And I think one of the answers I think to the question you were asking -- are we just looking for a number, or are we looking for something deeper? I think the U.K. adult autism survey really showed a lot of information about, you know, the lives of the adult autistic, and that's, I think, the real gem in that.

And that's the kind of stuff that for me I would like to see, you know, what works, what doesn't. We're getting a lot of great information from people like Paul Shattuck. As he watches people kind of go over the edge, it would be nice to kind of see the people who are in adulthood and kind of backtrack and say, you know, what -- I think in the U.K. one, the majority were unemployed. Most were unmarried. It'd be nice to have a large enough data set where you

could say -- for those who met sort of more typical standards of quality of life -- you could say what was the history that brought them there.

And that would give us -- to me, if we could do something like that -- it would give us that data set or give us the data to kind of feed that, I think that's the value, not just so much, you know, yet another prevalence number to throw out. So I think there is value in it.

Dr. Insel: This sort of brings back -- brings us back -- to John's point about rather than having that Question 6, which has kind of put a silo for adults, is to really weave it all the way through this in a way that we just didn't do when we started.

John?

Mr. Robison: I want to suggest one more thing be added to this iteration of the Strategic Plan. I'll even volunteer to take on writing it because I think it's an important thing. I think that when we

consider what the public and the community will get out of our finished Plan when they read it, I think that one of the things that we are criticized for is not delivering important critical information in a digestible form.

And I believe that the questions that most of the general public would want answered right in the beginning pages of our Strategic Plan would be in 2013: What have we learned about the prevalence of autism, and how it is acquired? And that could be one page of little bullet point references to studies on whatever. You know, on prevalence and causation.

And I think the second, the second page could be devoted to what are the highlights for 2013 and what we are doing about it. And that would be the achievements in 2013 in actual -- in therapy, in deliverable therapies to people. Because I think that that's what people ask. They say what are you people doing about figuring out how we catch

autism?

And I think that to some people, while I don't want to just dismiss the people who talk about vaccine and mercury and such, in listening to the comments today, I heard vaccine. And then I heard mentioned alongside vaccine, I heard lead. I heard aluminum. I heard mercury.

And I guess, I think it would be a strong, positive step for all of these people to say that we have funded study X, Y, and Z to look into these environmental causes. And I think that's important, and it ought to be there.

Dr. Insel: So John, let's hold on to that thought for another 5 minutes for the wrap-up section, and we'll come back to how we want to frame the ultimate message and what this thing should look like because we will have to have some overview comments and some concluding comments in the document as we put it together.

So hold on to that, and we'll get back

there in a few minutes. Are there any other comments on Question 7, specifically anything else you think Alison needs to put in, in terms of accomplishment, progress, breakthroughs since 2008, well, 2010 in this case? Dan?

Mr. Hall: Yeah, I wanted to mention one more capability that we have that I don't think too many people know about, which is the ability for us to translate a publication and the cohorts associated with the publication directly into data. And so you know, I think this offers a lot of benefit for corroboration of results that we're trying to promote to get scientists to do this so that others can easily see the underlying data associated with the publication.

This doesn't get us all the way back to the parents, as John spoke of early this morning, but this is a start where these publications and all the attributes and the specific subjects associated with the cohorts

and the outcome measures are made plainly available.

Dr. Insel: Lyn?

Ms. Redwood: I just wanted to make a comment there, and Cindy, help me out with this. In terms of infrastructure, there's a program -- I think is it a Tox21, Cindy -- that does high-throughput screening of different chemicals, and then it can look at the actual pathways that it hits. And then you could back that back up into the genes that control those pathways and maybe work at this from both sides, from the autism side and from the chemical side, to see if there are areas that intersect.

And so I don't think that program or that database came about as part of autism initiatives, but I do think it is something that we have an infrastructure that we should be trying to utilize. And even with Cathy, with the ADDM Network, we have these children that we've identified very thoroughly, and one of the concerns I have is that it's

constantly changing. Like, we're no longer in New Jersey, and we really needed to be able to follow that data longitudinally over time, but because these are recompeted, we can't do that.

So that's something I think that needs to be put in the Plan, too, is to keep those databases stable and not just assume when we see these different prevalence numbers in different States that we're either doing a better job or, you know, not as good of a job of identifying the children, but trying to sort of dig into what might be some other drivers in the area environmentally that would be unique to that particular population.

And we could also use the Toxic Release Inventory data by ZIP Code to try to drill into that, too. So we have that existing structure, but we need to build on it to be able to get more answers.

Dr. Insel: I can speak to the Tox21 question because that used to be in NCATS, or

the Institute that I used to lead. And the problem there is you need a cellular readout for high-throughput screening, and we don't know what that would be for autism.

We'd love to do something like that because it does allow you to screen very quickly for toxicants and to move very fast, but it's not really clear a best way to do that for this problem. We love to think about it because if we could come up with the right readout and something that could be high throughput that you'd have a fluorescent marker for, it would be awesome to be able to get a handle on that.

But I don't think we've had that in the way we have for lots of other cell systems. And we don't know enough really about what to interrogate here. Sorry?

Yeah, but even -- even in fragile X, we're still not sure what would be -- what would be the readout for a -- because it's not cell autonomous. We don't have an easy way to go after that. It's a good problem.

It's a good question to think about because if we could do it, then we'd be able to start the screening that everybody would love to have.

Other comments here? Coleen?

Dr. Boyle: Yes, Lyn, I was going to mention I don't know if you are aware of, but our Center for Environmental Health has an environmental health tracking program, which tries to accumulate and use States' ambient environmental data. And they have linked with our autism and our ADDM Network. So there's the ability to at the State level utilize those two systems as sources. So that's already actively undergo -- underway.

Ms. Redwood: Any idea when we'll have any findings?

Dr. Boyle: I can't answer that. I just know that it's clearly in the works.

Dr. Insel: Paul?

Dr. Law: I just had a comment about accomplishments, and that is that I think the international infrastructure for research is

very relevant to the U.S. because science is an international endeavor. And there are so many of our projects, the innovative projects that have been done in this country that are being modeled across -- across the world -- and I think that's a big accomplishment.

Over the past 5 years, there are all sorts of projects that have modeled different -- I hate to get into naming names, but there are ATN projects. There are IAN projects. There are projects that are modeling different things that we have done here, and it's very relevant to the scientific future of this community also.

Dr. Insel: So I think that's a great point, and Alison, I think -- I hope in the write-up, you'll reflect. And from my own Institute, with my NIMH hat on, I can tell you we don't have an NDAR for any of the other many areas that we cover, and we don't have an IAN. We don't have a lot of the infrastructure that's been put in place here over the last 5 years.

And we can still say that we need a lot more samples and we need a lot more individuals and we need a lot more use of it, but something has been built here which is really pretty exciting and exceptional. And again, I think we're all kind of used to it. And we've been talking about it for so many years, and we've maybe even been frustrated that it hasn't gone as fast as we would have liked.

But at this point, in 2013, there's a story to tell which is pretty exceptional for biomedical research areas. So I think we want to make sure that's captured in the write-up.

Dr. Boyle: I was going to say, Tom, I think that's a great idea, and I think we could all add, as representatives to agencies, you know, our own repositories. So, for example, we have -- I consider it a surveillance system that tracks environmental risk factors, you know, environment being very broadly defined through our SEED program.

That is a finite risk factor study, but we intend to continue that. So we're in, you know, Phase 3 of that study, and that's a repository. It's a repository of an environmental information, reproductive information, genetic information, and as that system grows, you know, it will be a resource to all.

Dr. Insel: So we want to make sure all that's in this summary.

Cathy, I think you're going to get the last word on this one.

Dr. Rice: Just to follow up on Paul's comment about the international interests, we also have an opportunity. WHO, the World Health Organization, held its first meeting on autism in September where they brought a range of people together from around the globe, and they're trying -- it was mainly a listening session to see what type of role WHO could play in bringing the autism community together.

And there were a few messages that were

very clear. One, needing to embed autism within the context of child health and developmental disabilities more broadly, particularly in lower resource settings where we can't have lots of specialized care to the same degree of, we need to have best practices that support children's health and development for the skills they need in that community.

But to the point about the work that has been done in the U.S. really was seen as a model. There are a lot of collaborators out there who are very interested in using and testing and doing research in low- and middle-income countries that this network may help us to tap into and think a little bit more broadly about some of the questions about diversity and disparities and variation in autism that we haven't really tapped into within the U.S. as much, but we have another network there. So that's a resource to think about.

Dr. Insel: Terrific. Okay. Alison, what

else do you need from us?

Ms. Singer: I think I'm good.

Dr. Insel: And you're going to do all this in two pages with a table someplace, right?

[Laughter]

Dr. Insel: All right. Congratulations, we made it through all seven questions. We're about 3 minutes past our agenda time. That's not bad.

I want to turn this over to Susan to talk to us about next steps, and then we'll make some summary discussion about where we're at and anything else you want to make sure that OARC knows or that any of the people doing the summaries will include.

Dr. Susan Daniels: So we have a few steps that are left before we finish an Update to the Strategic Plan for this year. One question that I have for Committee members is whether you feel that putting together separate drafts to talk about the funding issues versus the progress issues in

the field is still something you want to do.

We were originally going to do that along the way, but because of the shutdown, things have slowed down, and now we've already had all of these sessions, and we don't have all the write-ups. Would it make more sense to just do a single write-up, or does every group want to have kind of two sections?

Do one? So and for Group 4, you could just revise what you have. Okay. So I think that will make it a lot simpler, actually, because I think now we've all had a chance to put this all together.

So then next week I will send out directions and deadlines for the drafters for each group to go ahead and put together a draft. We'll give you a reasonable deadline to get a draft back in, and then we'll circulate them to the planning groups for review and comments, and that will include all of the outside experts as well to have a look at it.

After that gets put together, we will provide it to the chairs of the subcommittees to have a look to see if they want to make some unifying comments and just to get some people to look at the whole. After that, it will be circulated to the Committee, and we will plan for a phone call to do a vote and, hopefully, an approval because we need to have this Update text finished by December, by the end of December.

And of course, most people will want to go on some holiday trips and so forth at the end of December. So we don't really want to be working until December 31st on this. We want to get this finished probably in the first half of December.

We want to have a vote, and what we usually do is if on that call, we have final changes that need to be made, we will make those edits and then but consider it approved and voted on. And then in January or February, we will put out the final pretty plan on the Web site, but all the drafts will

be up on the Web in the meantime.

Mr. Robison: So will our Plan be done the next IACC meeting in January?

Dr. Susan Daniels: It will. The text will be done. I don't know if the whole -- I doubt that the entire PDF and all that will be ready yet.

Mr. Robison: We'll be done with our work on the Plan prior --

Dr. Susan Daniels: The work for this -- the work for this Update will be done for the 2013 Update.

Mr. Robison: Should we revisit that two-page summary thing that I asked about? Are we at the end now?

Dr. Insel: We're going to talk about that in a moment. So I see lots of concerned faces around the room. So --

Ms. Singer: Well, when we talk about the budget, can we refer to the “Other” as “Core and Other” because I think “Other” is extremely misleading, and it's a result of the fact that the objectives are based on

gaps and not really -- there's no place to put the core work. It's captured in “Other.” And so “Other” in some cases is 30 percent.

Dr. Susan Daniels: Perhaps -- something that might help, maybe OARC could help out a little bit with giving some preface information about the development of the Strategic Plan that we could, you know, pass around for review as well so that people could comment on it.

But to address that issue, we can also, I mean, if the Committee feels comfortable with changing that to "Core." I talked about it with every group on the phone calls so I think everyone has heard this conversation that “Other” just has not been the most descriptive term, and people would like to have a different.

So I don't know that we need to have a formal Committee vote about it, but if people feel comfortable, we can just change it to something like -- is "Core Activities" reasonable? So we could do that and have a

little bit of an explanation for those who might not be familiar with the Plan at the beginning but won't burden you with doing the initial draft for that.

Dr. Insel: There were a couple of other very concerned looks. Lyn?

Ms. Redwood: I think it was answered. I just wanted to make sure that the funding data was going to be incorporated into the final report, even though it was not going to be a separate piece.

Dr. Susan Daniels: The funding data? You mean all those tables?

Ms. Redwood: Yeah, the information in terms of how much we have funded toward the specific questions and --

Dr. Susan Daniels: We could. So OARC is also working on the portfolio analysis report, and those data were probably going to go in that report. So I don't know if we want to repeat it in two places or if we want to present it in two different ways.

Ms. Redwood: Well, even if it was just

sort of summarized in some way.

Dr. Susan Daniels: Oh, oh. I see.

Ms. Redwood: Not that it would be that granular.

Dr. Susan Daniels: Not all the tables. Because I think all the tables we'll put in the real portfolio analysis.

Ms. Redwood: Yes.

Dr. Insel: But just to be clear, I hope everybody is comfortable with this. I think for each of the questions, we need to start at least early on in the summary, whether it's two or three pages, there needs to be some comment about the funding.

We need to say that X dollars were going to this, to Question 7. We weren't going to do each of the objectives, the 12 objectives in each question, but an overall picture of what was invested. And then the portfolio analysis will really drill down to the specific objectives.

Dr. Susan Daniels: And depending on how that write-up turns out, if it makes sense to

maybe have a place for those tables in there, we can always work the tables up so that they look nice with the text and are referenced. It might take looking at how those drafts look before we do that.

Ms. Redwood: And maybe even something at the very beginning, too, that addresses the history of the Plan, like you were saying, that includes the tables --

Dr. Susan Daniels: Right. I think that our Office could take a first stab at that.

Dr. Insel: Yeah. So that raises this other issue that John brought up then. What are the framing issues for the write-up, and what are -- I mean, as I listened today, there were a series of sort of cross-cutting themes. You started us out with one, John, when you talked about sort of managing expectations, and Scott brought up about ethical issues.

And we heard in the course of the day sort of themes like not waiting for behavior to develop the diagnosis or to do detection,

but coming up with changes that might be much earlier. We heard about the need for not just research, but for measurement. And that was kind of a theme that kept coming up that almost every question we needed far more precise measurement tools than what we've got.

Certainly the lifespan issue that you introduced again, John, about creating some way of going throughout the Plan on issues related to adults, as well as children, which is something that's changed over the last 5 years in the way I think the Committee is thinking.

And then this very important comment that we heard, especially for 3, 4, and 5, and a little bit in 6, of moving practice into research, kind of getting out of that kind of academic setting using communities as the base for the science and engaging a much, much broader public in the scientific effort, something that's happening in lots of other areas of biomedical research, but it hasn't

quite happened in quite the same way here, and that seems like the next big opportunity.

So we could provide some sort of an overview of some of those issues. This last thing that you brought up about doing a quick summary on prevalence and mechanisms, I guess from my own read, that seems like it could be in the Plan itself since we have sections on etiology. We have sections on prevalence. I think there's a place where we can say that clearly.

But I would encourage all of the chapter writers, if it is going to be two pages, to make it very accessible and to make these two pages high level, kind of very clear, and so somebody can see this and basically after you've said we spent $190 million, the public can see what has come out of that. And then to perhaps finish with where the next set of opportunities will be as well

Is that, John -- I don't know if that's kind of what you had in mind, but I think if we can have a document that's succinct at the

end of the day that really does provide the Update in the sense that the Committee asked for, which was the accounting but at the same time provides some overview of where we are in the field and where we're going, that would be great.

Mr. Robison: Well, I guess the thing then that we would need for that is we would need to put together a summary of advances for each of the questions, which we really didn't do this year.

Dr. Insel: Yeah, but that is just what we've done all day. So we've got -- I have a list of, like, eight pages of what has happened since 2008 on each of the questions.

Mr. Robison: Yeah, I mean, I guess I've heard what has happened since 2008. I just -- you know, what I haven't heard is a list of, say, papers that we would cite for things that came out in 2013, and I think that's probably important backup.

Dr. Insel: Yeah, it is. So I guess we will do the summary of advances but you know,

I think what I heard from the Committee when we talked about this before -- and I thought it was really an important point from several of you -- is that we didn't want papers to be the outcomes, that we thought it was really important in this document to go to a deeper level to say, you know, there may have been 100 papers that came out of an investment of $100 million. But really we're not interested in papers. We're interested in products. We're interested in breakthroughs and discoveries and insights that in treatment, something that really changes the world for people with autism.

And I think the papers will come out in the course of doing the summary. But I don't think we want to weigh this down with lots of references and lots of papers for backup.

Mr. Robison: All right. I guess I was one of the people who argued that we needed to talk about the real delivered results and not the papers, but I guess I didn't -- I just didn't think we would drop the papers

totally, you know? That's all --

[Laughter]

Mr. Robison: but it sounds like --

Dr. Insel: You were so compelling. I think you convinced us that. So yeah, don't go back.

Yeah, but I think Lyn had the same comment at the previous meeting that while papers are important, we all got that, we wanted to -- we literally wanted to know what have we learned. And that was something at a kind of a different level. It was the integration of the literature in one place.

Each year we do the summary of advances. Each year, we have the list of top papers. But this is something a little more accessible for the public -- to say so this is what we've gotten over the last 5 years.

Ms. Redwood: John, were you thinking of, like, maybe an executive summary to boil down each of the 2 pages for the 14 pages?

Mr. Robison: Yeah, that's basically what I thought about. I thought about like a

couple page executive summary for the whole report because I figured that a lot of the laypeople who would read it would not make their way through our whole report, no matter how human friendly we made it.

And I just thought that we ought to take what are the biggest questions families stand up here and ask us, which are how are we detecting it and what are we doing about it, and we ought to distill that into two pages at the beginning. And I guess I still think we could do that productively.

Ms. Singer: I think we usually -- I mean, we usually do do that. At the beginning of each of the Updates, there's usually a two-page introduction that talks about the cross-cutting themes and I --

Dr. Insel: Right.

Ms. Singer: -- would assume that we would have that.

Dr. Insel: Yeah, that's what I was trying to say. I didn't say it well, but that's the idea here.

Mr. Robison: So are you saying you're going to write it then, Tom, so we don't have to worry about it?

[Laughter]

Dr. Insel: Why did I look at Susan? You know, if we can get the summaries in place, I am going to be completely out of pocket after December 15th. So if we can get everything done before then, I'll definitely help with the overview. But --

Mr. Robison: I'll work on writing it, too.

Dr. Insel: We'll do it together.

Mr. Robison: All right.

Dr. Insel: It'll be fun. We did that -- last time we did that it came out pretty well, I think. So we both got in trouble, which is a good sign.

[Laughter]

Dr. Insel: Other summary comments or other thoughts about what you want to see in this final document? And I want to remind you that when we talked about this, this is so

different from what we've done in previous years because people really wanted this to be our chance to show deliverables. It's the accounting exercise.

From my perspective, I think that the portfolio analysis took us a long way in that direction, but we need to now put words around that.

Anshu?

Dr. Batra: I guess I just wanted to clarify that this would be a document to educate -- educate the public about what we've learned in the last 5 years but also then how we are applying it in practice. I hope that that's the inference here?

Dr. Insel: No, I would say --

Dr. Batra: It's not?

Dr. Insel: -- you know, so the statutory requirement is a Research Strategic Plan and an Annual Update. And what I heard from the Committee when we started this process was let's look at instead of adding -- instead of revising the Plan at all this year, we'll

hold tight with 78 initiatives, and we won't change any of them, but let's look at what we've accomplished up until now on the research side in terms of what is the science telling us that we can now report out on, having a made a fairly large investment.

Dr. Batra: So where in this could we put in something? Could it be aspirational goals or next steps that now we have all this wonderful knowledge, and what do we do with it?

Dr. Insel: I wish I could say that we have all this wonderful knowledge. I think what we heard today is --

Dr. Batra: Well, today has been a discussion of all the wonderful knowledge we've obtained.

Dr. Insel: Yeah, well, there will be, I think, an opportunity in the overview to try to capture, as John was saying, because 90 percent of people are only going to read the executive summary, and the other 10 percent I can't imagine why -- who they are. So we will

have to -- I mean, that will be our job is to put something in there that is a takeaway so that people can get a sense of really the state of the science.

Where are we currently in 2013? And certainly, one of the implications will be that there's still a lot to do. We've got some progress. We've got areas that look really promising. We've got new tools. We've got some great resources to work with.

The infrastructure is now largely built in many areas, but we still need to deploy it, and we need to -- we need to have something that's more user friendly, something that's actually actionable from so many of these areas.

Lyn?

Ms. Redwood: I was just going to say, Tom, that's a really good discussion for our January 15th meeting in terms of where do we go from here? This is where we've been the last, what, 5, 8 years? And where do we want to go from here?

So I think that's the way to take this information, these exercises that we've painstakingly gone through the last few months and use it to inform where we go and include guidance to clinicians in that and to families.

Dr. Insel: Great idea. Let's put that on the agenda for January. Do we have a date for the meeting?

Dr. Susan Daniels: Yes. It's up on the Web site, and I hadn't wanted to confuse you all by sending you more dates as we had the shutdown, and we changed the date of practically everything. But we have a date for January. It's January 14th, which should avoid any possibility of us getting cancelled because of a shutdown because that would be the next day.

So we should be able to hold our meeting unless there's a giant blizzard.

Dr. Insel: That's almost a guarantee that we'll have a giant blizzard. Scott?

Dr. Robertson: Please bite your tongue.

Don't say things like that. We're going to have something that happens.

But related to the whole accounting thing, is the Plan Update going to be able to take in account not only the good improvements that we had, but some of these, well, we haven't made as much strides in the last 5 years as we should have?

Because a true accounting should talk about both good things that happened and where we haven't really done as much as we said we would do, including things like I said where it's written in surveillance that we were going to do that, and it didn't happen yet. So I hope that the Plan Update can make sure to take into account some of the things that we've talked about today where we've looked back in the last 5 years and said, well, we haven't made as much stride as we should have in there.

Because if it only talks about where we've made improvements on, that's not -- that's not a real valid reflection of the

tableau and of the where things stand right now. And that's not doing justice or fairness that when folks read the document, it will be an accurate reflection where things are, and especially if it doesn't reflect, you know, some of the challenges and concerns that we've had where things have not improved as much as they should.

So is that the accounting will take into account, you know, some of these concerns of things that have also not happened as well as they should have?

Dr. Insel: Well, I know that Question 4 will because I'm writing that one. I would assume that everybody will take that kind of an approach. It's going to be -- I mean, we can actually provide a fairly good template for this. I think we've already done that in some form, which is something about the funding, something about what's been the return on that investment, and something about what hasn't happened.

And then I think a section at the end

about opportunities and how they -- you know, what's the landscape like now and what to think about going forward. Because there are so many areas where we wouldn't have even known to ask the question in 2009 or '10, and now we have a whole new set of opportunities that we shouldn't ignore.

And one of those, I think you heard this from Alison, was that maybe some of those original objectives aren't even really worth pursuing anymore. And that would be important to note as well.

In a way, I think what we're talking about is even though we decided not to rewrite or revise the Plan this year, this will serve as a basis for either our group or another group, if there's another IACC after September of 2014, to work from for an actual revision.

Susan?

Dr. Susan Daniels: On the phone calls, we also did go through many of those types of items that you just mentioned. And so we have

them summarized for you in the table to some extent. And so you'll have all of that information. So even though that wasn't really the focus of today's meeting, you did go through some of that on the previous phone calls.

Dr. Insel: Yeah, I feel like I have to apologize a little bit about that, Scott. Because you know, I'm so aware, and you could even see it in the way that the slides were set up, that we're so conscious of all the needs and the unmet need and how urgent the problems are that I feel like we don't spend enough time recognizing that there really has been progress.

So all day long, I feel like I've been pushing you to tell us about the part of the glass that's half full, and I only did that because I just think if we don't focus on that, we won't actually recognize it, and then people assume that nothing has happened. And I get that for a lot of people, not enough has happened. But in fact, on every

one of these questions, I think you'll see with the write-up, and we heard it today, there has been substantial progress.

And still much more to do, but we're on a really, really good path.

Okay. Any final, other thoughts? Coleen?

Dr. Boyle: So I personally wanted to thank Susan Daniels and her crew for what I would consider a Herculean task of really getting all of us organized, and I thought we were going to sort of take a new course after the break -- well, I call it a break. It was a furlough.

But I mean, you kept us on task, and you kept all the phone calls going, and so I really appreciate that in terms of --

(Applause)

Dr. Insel: They are now going to be asked to fix the health care Web site, I understand.

[Laughter]

Dr. Insel: That's their next task. But that's not until after December 31st. First,

we have to get this done, and that's their next task.

You guys have been great today. What a fantastic conversation all day. I really appreciate your engagement with this. For the experts who came, many of them from very far away, thank you so much for your help and for helping the IACC on this important task.

Still have a little bit more work to do. We'll do that electronically. I want to wish everybody a Happy Thanksgiving in another couple weeks, and we will be in touch.

Thanks. We're adjourned.

(Whereupon, at 4:48 p.m., the Interagency Autism Coordinating Committee’s 2013 IACC Strategic Plan Update Workshop adjourned.)