U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

FULL COMMITTEE MEETING

TUESDAY, JULY 15, 2008

The Committee met in Conference Rooms E1 and E2, Natcher Building, National Institutes of Health, Bethesda, Maryland, at 9:05 a.m., Thomas Insel, Chair, presiding.

PRESENT:

THOMAS R. INSEL, M.D., IACC Chair, National Institute of Mental Health

DELLA HANN, Ph.D., IACC Executive Secretary, Office of Autism Research Coordination, National Institute of Mental Health

DUANE F. ALEXANDER, M.D., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

ELLEN W. BLACKWELL, M.S.W., Centers for Medicare and Medicaid Services

JUDITH COOPER, Ph.D., National Institute on Deafness and other Communication Disorders (For James F. Battey)

MARGARET GIANNINI, M.D., F.A.A.P., Office on Disability, U.S. Department of Health and Human Services

LEE GROSSMAN, Autism Society of America

GAIL R. HOULE, Ph.D., U.S. Department of Education

PRESENT (continued):

YVETTE M. JANVIER, M.D., Children's Specialized Hospital

STORY C. LANDIS, Ph.D., National Institute of Neurological Disorders and Stroke

CINDY LAWLER, Ph.D., National Institute of Environmental Health Sciences

CHRISTINE M. McKEE, J.D.

PATRICIA A. MORRISSEY, Ph.D., Administration for Children and Families

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

STEPHEN M. SHORE, Ed.D., Autism Spectrum Consulting

ALISON TEPPER SINGER, M.B.A., Autism Speaks

EDWIN TREVATHAN, M.D., M.P.H., Centers for Disease Control and Prevention

PETER van DYCK, M.D., M.P.H., Health Resources and Services Administration

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9:05 a.m.

CHAIRMAN INSEL: We're going to be a little slow getting started here this morning. We'll be slow but very safe. A couple of people walked in and said, "This is definitely not the Reagan Building."

Welcome to the NIH campus for those of you who have not been here before. We've got a pretty full agenda, a number of things we need to address in the course of the day. Lots of scientific progress going on in the community and we'll have a chance to capture some of that in the afternoon.

There will be two sessions, one from Mark Bear talking about work on Fragile X, and another from Walter Koroshetz from NINDS to talk a little bit about the mitochondrial meeting that was held a few weeks ago.

Also, in terms of scientific

progress, there is a summary that is in your folder which is one of the many things required from the Combating Autism Act that we each year have to report out on progress made in the previous year. This is the summary of advances dated July 1st and we will come back to this.

You will remember that the format of this was something we discussed last time so this is now filling out that template that you heard about from Diane Buckley and we'll have a chance to revisit this later.

Among other changes you'll notice that Dr. Della Hann has joined us as Exec. Sec. for the committee and she will also be involved in managing the autism team, the autism effort so she'll be the person who will be replacing Dr. Joyce Chung who did such a spectacular job for this first year. Dr. Chung is going back to her day job at Georgetown University where she is in the Department of Psychiatry.

The only other informational point to get started with was to let you know that we have also hit a new phase for NDAR. This is the National Database for Autism Research which just about two weeks ago released a version 1.5. This is now being used. It started on the first version for capturing our intramural effort. It's now getting all of the data from the Autism Centers of Excellence.

The first cohort of those centers, the first seven are working with NDAR now to load up data. The second group will be starting in January so we hope very soon to have all of the data in a format that will be easily reviewed by anyone.

Why don't we do a quick round of introductions while we are waiting for the few minutes who are still on their way here. I feel sorry for some of them because in addition to the problems with security for some people who were trying to come yesterday

the air traffic was a mess.

I know getting into Washington because of the storm the night before and yesterday morning was really horrendous. This has not been an easy trip for some people but we'll be understanding.

Duane, do you want to start with introductions?

DR. ALEXANDER: Yes. I'm Duane Alexander, Director of the National Institute of Child Health and Human Development at NIH.

MS. McKEE: Christine McKee and I'm a parent of an eight-year-old girl with autism.

DR. LANDIS: Story Landis, Director of the National Institutes of Neurological Disorders and Stroke.

MS. SINGER: Alison Singer, Executive Vice President, Autism Speaks and mother of an 11-year-old daughter with autism and sister to a 44-year-old man with autism.

DR. LAWLER: Cindy Lawler,

Extramural Program Director at the National Institute of Environmental Health Sciences.

MR. GROSSMAN: Lee Grossman, President and CEO of the Autism Society of America and the dad of a almost 21-year-old young man with autism.

DR. COOPER: Judith Cooper, Deputy Director, National Institute on Deafness and other communication disorders here for Jim Battey.

DR. JANVIER: Yvette Janvier, developmental pediatrician in New Jersey.

DR. VAN DYCK: Good morning. Peter Van Dyck, Director of the Maternal and Child Health Bureau.

DR. HANN: And Della Hann. I'm currently the Executive Secretary for this committee and also Director of the Office of Science, Policy, Planning, and Communications at the NIMH.

CHAIRMAN INSEL: And Tom Insel, Chair of the Committee, and Director of NIMH.

We have two quick things to look at in terms of review and approval. I'm stalling a little bit waiting for a few more people to come but we can begin to look at these anyway.

First is the autism meeting summary. It's in your folder from the previous meeting of the IACC. This is the May 12th meeting. I need to know whether you have any questions, comments, changes. If there are no suggestions for changes, is there a motion to accept the minutes as written?

DR. ALEXANDER: So moved.

CHAIRMAN INSEL: All in favor? So done. Anyone opposed? Story, you're okay with that? Okay. All right.

The second document is the summary of advances in ASD research that I just mentioned a moment ago. It looks like this. This is the one that you heard about a bit last time. It's one that we need to send forward to capture the last year from 2007.

You will remember that we

formatted this to go along with the six questions that are part of the strategic plan. If you will take and look and if you have any comments, questions, or suggestions. Hearing none, can I get a motion to approve this document?

PARTICIPANT: So moved.

CHAIRMAN INSEL: Second?

PARTICIPANT: Second.

CHAIRMAN INSEL: All in favor? Anyone opposed? Abstentions? I think the document passes. Thank you.

Now, the next thing we wanted to do is to go through the report from the Services Subcommittee. Ellen Blackwell was one of the people who is standing in the line outside the building. Perfect timing.

So, with that spectacular entrance, Ellen and Lee, as you recall, were asked to lead an effort for a Services Subcommittee and they have done that with participation from many people from the IACC

as well as from others. I will turn the floor over to the two of you to give us a quick summary about where this effort is going. Thanks so much for getting here exactly on time.

MS. BLACKWELL: Okay. Perfect. Well, we met for a full day at the Autism Society offices. Thank you, Lee. Thank you to everyone on the IACC who attended virtually and in person and also who has volunteered to participant in this effort.

That day Lee and I were there, Lark, Gail, Christine, Cindy, Julia Whitney represented Ed from the CDC. Bonnie Strickland sat in for HRSA. Della was there and Azik. We did take the time to go over the initial 41 workshop initiatives for the strategic plan. We determined that about 13 of them were related to services, which was interesting.

If you take a look in your packet, you will see that one of the things that we

decided to do that we talked about at our last meeting was to issue another request for information similar to the one that the IACC issued in terms of preparing for the strategic plan.

The draft should be in your packet. It looks pretty similar to what we issued before. One of the things we decided to do in the Services Subcommittee meeting was to try to give the public some examples of information, particular ideas and topics that we thought would be good.

Under information requested, No. 2, these are the areas that we thought we would solicit information on. If everybody is okay with this, we would like to go ahead and get it out pretty quickly. Does that sound like a reasonable course of action? Okay, I'm going to take that as a yes.

CHAIRMAN INSEL: So let's actually assay this for real. I'm just curious because we do need some feedback. Does the group want

to go ahead with putting out the RFI? All in favor? Opposed? Okay. I think they want to do this.

MS. BLACKWELL: Okay. Great. One of our thoughts was that we also had spoken previously in this meeting and at the Services Subcommittee meeting about perhaps engaging in a series of town hall meetings to talk about services and supports. We think that before we do that it would be good to get this out and get the response back in.

Another task that we undertook on the 13th was to start going over the autism roadmap that was prepared by the previous IACC and really focus with the idea of looking at that roadmap on just a handful of items that we think we can get done in the next four years or four-and-a-half years or whatever it is we have left in our tenure.

As part of that I'm really happy to be able to talk today about the fact that last week CMS issued a task order on services

research for autism specifically. That has gone out. We have already gotten some interest.

It was issued to our XRAD contractor list which is a way that we solicit research proposals very quickly for research that we want to be on the fast track. It really has four pieces. The first piece is to take a look at evidence-based services and supports for children, youth, and adults with autism.

The second piece that we are hoping to get is a look at -- sort of a focused look. We are only permitted to solicit information from nine states at a time so we want to go out and talk to nine states and figure out what's going on with people with autism. Again, the whole array of ages and look at a gap analysis and talk to the folks in the states.

The third piece is to start the development of models for services and

supports for children and adults with autism. The fourth piece is something that Lark brought up at our Services Subcommittee meeting which is the idea of having a webpage where folks can go to just take a direct look. You know, really link into research articles. Really just have a direct way to go into the federal government and get information about services and supports on autism. That project is in process now and we hope to have proposals back by the middle of August.

The other question I have is I think, Tom, you had mentioned that you wanted to devote the November meeting to services? I wasn't sure where you were with that but do we need to ask folks at the table today what in particular they're interested in, what areas of the services?

CHAIRMAN INSEL: There will be two big topics for the November meeting. One would be the final approval of the strategic plan that will come back to the group then.

The other topic that we talked about at the last meeting was taking some time to really hear more about the services agenda.

I guess it's a question of whether the subcommittee feels like the timing is right and what it is you think would be best to do at that point. I'll turn it back to you, Lee. What is your sense?

MR. GROSSMAN: We had discussed that and actually the entire discussion all day was very productive. We went around the table and it was remarkable to all of us what the agencies are doing to address autism.

For some of us we feel the pressure of looking at this November deadline as something that is going to be hard for us to meet but, yet, something to hold our feet to the fire to come forth with a document or a plan that we can start working on.

The RFI is one of the implementation aspects of putting a plan together. We are also going to go back and

review the roadmap that already exists and that was one of the tasks that all of us had to see what our agencies can do to respond to the roadmap that is out there. I believe we are planning on having a series of meetings and perhaps town hall meetings throughout the fall and we'll cobble this report and plan together by the November meeting.

MS. BLACKWELL: Did you mention, Lee, that you had just returned from your annual meeting in Orlando?

MR. GROSSMAN: I did not mention that.

MS. BLACKWELL: Okay.

MR. GROSSMAN: There was quite a bit of discussion about IACC at our conference. The ASA annual conference was last week. We had about 2,100 people attending there. There was quite a bit of discussion regarding IACC.

Obviously of the 150 presenters that we had I would say that probably 110 were

discussing service related issues so that certainly is a priority among our constituents as they see this as the most critical need for the autism community.

Certainly I think that anything that the IACC puts together to address the service needs, to improve and expand services that already exist will be looked at as a very positive step.

MS. BLACKWELL: The only other thing I have to add is that we at CMS continue to be besieged by states really looking for ways to serve people with autism. Every week we have a technical assistance call or a state coming in with a proposal. We have some really interesting stuff on the docket now.

A managed care proposal for adults and also Nebraska has come in with a proposal to serve children through the University of Nebraska, I believe. So, you know, it's just nonstop. It's very good that we're looking at services research not just at CMS but within

the context of the entire IACC. It's very important work.

CHAIRMAN INSEL: Let me ask you from the committee's perspective for those of you who are not part of the subcommittee, is there anything that you want to convey to the group or want to ask for for the November presentation?

MR. GROSSMAN: I would like to add that I think that HRSA just came out with a medical home document. It's available by online in the pdf version. I think that's a very important document.

It was related to the Medical Home Project that they've been working on but there were some very interesting data that was presented as well as concepts regarding autism one of which that I found most enlightening was looking at autism as a chronic medical condition.

It's great to have an official federal document that was putting that out

there for discussion, debate, and actually what I would consider a position. That is something that this Services Subcommittee should be looking towards as we try to move the service agenda forward.

I think a statement such as that looking at this as a chronic mental condition have huge public policy implications in terms of us going after insurance reimbursement, for example, long-term care, and other factors. Those are the types of things that will be encouraging and compiling to bring forth to develop an entire plan on services.

MS. BLACKWELL: I think that's it.

CHAIRMAN INSEL: Okay. So we will plan to hear more in November. If there is other input needed from the group, make sure that we have a chance to hear about it at some point today. I guess the one thing I would convey from the previous discussions we've had is the increasing need to focus on adolescents and adults. I'm sure that's already been on

your agenda but it's something I know people want to hear about in November.

All right. Let's move on with the agenda. Thanks for that report. We are going to go to Dr. Judith Cooper who will report out on the Strategic Planning Workgroup meeting that was held very recently, I think last week. This, again, is the follow-up to the discussions we had last time about the strategic plan.

You will remember that where we left off was after come debate about how to go forward we decided that the NIH, CDC, Autism Speaks, Assignments Foundation, and DoD would do a SWOG or SWAT analysis looking at strengths and weaknesses of current portfolios and that was distributed to you. You should have seen that by now.

There as an agreement that the autism team would work on the vision, mission, and aspirational goals and circulate that for approval which has happened. We wanted to go

over the 41 initiatives and potentially consolidate. I think Dr. Landis said 30 would be a better number than 41 and so there was some effort to do that as well.

Then there was a draft plan that was put together by July 1st and this was taken to the workgroup, the same workgroup that had met earlier to help on identifying priorities and budgetary requirements. We brought them back to be kind of first public reader on the draft plan that we've got leaving out the budgetary requirements which will be happening at a later date.

Judith, you can take it from there.

DR. COOPER: Okay. Thank you, Tom.

All right. Good morning everyone. So my task is to tell you a little bit about the meeting that was held last week. It was just July 8th. As Tom said, it was to give the working group a chance to comment on the

strategic plan, the draft.

This was not a face-to-face meeting. This was a webinar. It was open to the public so we had more than just a working group. There were about 76 people who participated. That included the working group and some members of the IACC and then even some members of the public.

One thing I want to say is we want to give you a flavor of what kinds of things were talked about last week but we did not achieve any sort of consensus. We didn't take any votes. What I'm going to share with you are just comments maybe that one person said, maybe several people said. I just want to make that clear.

Just to refresh your memory, these are the folks who serve on the working group. We met once before in April and all of those individuals, I believe, all of them are on the phone.

Okay. A few comments about the

plan. As Tom said, it is a draft because it doesn't include the budgetary information which is a requirement. We still need to have the draft go out for public comment. In keeping with what Lee and Ellen were talking about, the services research is included in the plan but services provision is not.

There were a couple of themes that came through in the meeting. One was the need to enhance and clarify language to capture more effectively the values and goals that you, the IACC, have put forth. There was a sense that we needed to strengthen the integration of cross-cutting themes within the objectives and we needed within the plan to more effectively convey the sense of urgency that we hear expressed by you and by the ASD community.

So here are some of the individual comments that the committee had with regard to our introduction and our cross-cutting themes. If you need to follow along, of course, the

draft plan is in your packet.

Some of the comments included a need to strengthen the sense of urgency. We talked about that and the importance of prevention. To describe the need for cutting-edge science. Some individuals thought that we needed to highlight early detection more, both prenatal, postnatal, and early childhood.

There were some who thought there needed to be an expansion of heterogeneity to include disease, risk factors, treatments, and intervention and, of course, balance with common features. Some thought we needed to highlight more our partnership between the ASD community and the research communities.

You will remember that our first question is, "When should I be concerned?" So we asked the working group what would you like to say about what's in the plan with regard to that question. Some of the comments included a need for collaboration with existing culturally competent resources to facilitate

the recruitment in under-served communities.

Some thought we needed to strengthen the biomarker discussion to include post-natal, genetic, and gene by environment research. An initiation of immediate biomarker research was suggested by some.

Early detection informed by linking developmental trajectory and biological processes was also discussed.

Some thought there needed to be a discussion of the detection of regression in this population.

What about question 2, "How can I understand what is happening?" Some of the individual comments included the need to highlight the importance of immune and other medical problems in understanding ASD. Some suggested expanding the access to biospecimens to include other tissues beyond brain such as skin fibroblasts. How about sharpening the focus of the second short-term objective, some said, to include immune and metabolic

interactions within the CNS.

Some working group members suggested expanding a long-term objective to include youth and adults and extend the time frame of one of the initiatives to 2030 that would allow us to examine how the symptoms change over time. Some suggested that we needed to balance the aspirational goal to include interventions applicable to a wide range of individuals.

Question No. 3 is, "What caused this to happen and can this be prevented?" The individual comments included a need to expand the environmental factors section in what do we know and the suggested example was that toxicology resources and informatics infrastructure as avenues for collaboration in the study would be advised.

It was discussed about whether we needed a specific objective on vaccine research or we have currently some broad wording about environmental factors and there

was a discussion about whether that really did capture the issue.

Some suggested that we include an objective on developing cellular high throughput systems. Others said testing the impact of environmental factors using cell lines from individuals with ASD was needed. The development of international resources and perspectives might be expanded said some. One individual suggested that we discontinue the use of the word "preemption" which is in one of the objectives and stay just with the word "prevention."

Question 4 is, "Which treatments and interventions will help?" Some of the individual comments we got on that question were that we needed to expand the aspirational goal, to also focus on strengthening adaptive and positive outcomes in this population. Some said we needed to balance a discussion of possible treatments to give more support for the study of treatments in current wide use by

parents and families.

Others suggested emphasizing the need for methods and designs that will allow us to identify what works best and for which individuals. This would have two advantages. One, it would help identify subgroups as well as possible mechanisms and it will encourage bedside to bench translational research, a bit of a reversal in translation. Some suggested that we needed to strengthen the emphasis, as Tom had said, on school-age adolescents and adulthood treatments.

Okay. Question 5 is, "Where can I turn for services?" Some of the comments we got about that question included within the "What We Know" section. It was suggested that we replace what we've got written on prevalence and put in something about services and communities of care and support.

Some suggested that we even revise the aspirational goals to read as follows, "Communities will implement high-quality,

research-based, and cost-effective services for supporting quality of life across the life span for individuals with ASD." As we saw in one of the other discussions, some thought we ought to highlight again the partnership between the ASD communities and the research communities.

It was also suggested that we add a short-term objective to assess how variations and access to services post diagnosis affect families. Some individuals on the group suggested that we expand the second long-term objective to include process analysis about what allows a model to be effective.

Others suggested adding an objective to build infrastructure resource that would systematically record families experiences= to interventions and treatments.

Okay. The final question is, "What does the research hold?" I'm sorry, "What does the future hold?" We had just a

few comments, a small discussion on that question. Some suggested that we add a long-term objective to study the effects of early intervention programs on adulthood including the study of how cost of early intervention might affect adult needs and costs.

Finally, it was suggested that we might expand the comments to include mention of potential opportunities to partner across agencies and into the private sector to launch more research on an adult population.

Then the working group had a few little comments about just the implementation of the strategic plan. One was, of course, about the budgetary requirements which weren't in the report. They thought it was -- they talked about it would be important to determine who is going to provide funding and which projects and what mechanisms would be used.

They were interested in learning about and establishing a process for

prioritizing the treatment and intervention research focusing on determining how to identify what works best and for which individuals.

Then members of the working group certainly -- well, the ones who spoke up indicated that they were willing to participate in any and all of the next steps. That pretty much gives you an idea that a lot of people had a lot of ideas. Some people didn't say much at all so it just gives you a smattering of the issues that were discussed and raised.

I think what we are going to do now that you have sort of the overview is Tom is going to lead a discussion as we go through those specifics again and get a sense of what the IACC, which has the ultimate responsibility for the report, of course, has to say about some of the suggestions.

CHAIRMAN INSEL: Great. Thanks, Judith. Maybe you should stay up there so we

can help to go through some of the slides. Let me also add that, as Judith mentioned, there were many members of the public who don't serve on the workgroup but who could listen in and they were asked -- though they couldn't speak during the meeting, they were asked to send in recommendations or suggestions. We tried to capture those. They are in your folders. It says, "Comments from the July 8, 2008, SPWG Webinar."

In addition, we have letters from Lee Grossman at ASA, from Peter Bell at Autism Speaks, and from Theresa Wrangham at SafeMinds and also endorsed by other groups as well that are in your folders that also represent their recommendations based on what they heard or what they thought needed to be included in the strategic plan.

As Judith just mentioned, this is ultimately your plan so you could take all of this under advisement and you are welcome to make any changes. You could take some of it

that is really, I think, going to be important to dig in a bit and to walk through. I want this strategic plan to be the clearest and most compelling document possible.

This was a group that got very engaged with the process and I think they were really trying to be helpful to give us a sense of what worked and what didn't work and what they thought was missing.

Sometimes what was just unclear I was really intrigued by some of the ways they read statements that we had in there which were not at all what we had intended so it's going to be very important to take those kinds of comments and clarify what we've done.

Before we jump into -- actually, why don't we go back to the next slide. Let's go to the one that has the cross-cutting themes. Okay. Yes. Before we get into the specific comments, any general thoughts about this?

You all have had the plan but

actually we haven't talked about the draft you have. You are looking at the same draft that the workgroup looked at last week and we use them just really as your readers, your first readers to give you a kind of quick overview and review of how this works.

Before we take their comments into consideration, any comments from the group that you want to make about the plan as it sits? Remember what we want to do today is to get this plan to a point where we can put it out to a broader public so there will still be opportunities to make revisions.

We are going to want to incorporate what we hear from an RFI when we put this thing out in the very near future. Before we put it out we want to make sure we have captured what you feel about it and also any of the comments that came from the workgroup that you think would improve the plan.

Lyn.

MS. REDWOOD: Hi, Tom. Can you hear me okay?

CHAIRMAN INSEL: Yes.

MS. REDWOOD: I think the comments that were made by the workgroup are excellent and they are right on. When I look through these cross-cutting themes I just felt like there were several things missed in what I had reviewed previously from the RFIs and the town hall meetings. I think there needs to be more focus on the environment. I think there needs to be some mention of co-morbidities and multi-organ system impairment.

I just really wanted certain that these cross-cutting themes were really representative of what we had heard in the past so I would like to see a little bit more work done on these cross-cutting themes and to include the excellent comments that were made by the workgroup.

MS. SINGER: I agree with what Lyn is saying. I would also add to what the

comments are up on the board that in the section for earlier detection we expand to include earlier detection and early intervention.

I think we made a big point when we developed the six-question format to make sure that the plan was focused on real people's lives and focusing the science on what real people need. I think we want to make sure that we are really honing in on the fact that one of the reasons we want to detect autism earlier so that we can intervene earlier to both prevent and preempt.

I think when we get to that section on preemption I have a couple of things to talk about with regard to preemption which I can say either now or hold for the session --

CHAIRMAN INSEL: Why don't we hold that. Your comment would be that this early detection piece involves the intervention as well as detection. So what we'll do -- what

we want to do here is to grab whatever your thoughts are.

As I said, we had not incorporated anything from the workgroup yet because it's up to you to decide what part of that is worth incorporating. There are all kinds of opportunities here.

Christine.

MS. McKEE: We mentioned twice in the early sections about the availability of the increase in resources. We said in the introduction and then talk about it in the public/private partnerships how research is coming along. We have made great strides because of our increase in resources.

At every meeting I keep hearing there is no new money and so I would like to have some indication in there that although we have increased our resources a little bit, we have gone from nothing to a small amount instead of saying that we are on course.

MS. REDWOOD: Tom, would it be

possible to go back to the vision and mission statements? I noticed there had been some revisions in those from our last meeting. Then there was an addition to the vision statement that the plan will set forth the standard for public-private coordination and community engagement.

It just seems to me that is captured down in the core values when we discuss partnership and action. I was just sort of questioning whether or not that should be part of our overall vision statement.

Again, I just really feel strongly that somewhere in there we really need to mention prevention either in the vision or mission statement because that is the overall mission of the National Institutes of Health and also the National Institute of Mental Health when you look at their vision and mission statements. I think we are really missing something if we don't have that in there as one of our goals.

CHAIRMAN INSEL: Comments about that?

MS. SINGER: I agree with exactly what Lyn said. I think we do need to emphasize prevention, preemption, as well as treatment. I know again on a future slide when we get to Section 4 the group talked about prioritization of the treatment section but I think this group has at the last few meetings talked about the importance of prioritizing the section on prevention and preemption.

DR. SHORE: I'd like just to comment. I would like to see the word "ethical" put in front of prevention.

CHAIRMAN INSEL: A lot of what you see here is the result of taking comments from many, many different sectors. At least we have heard some real concerns from parts of the public about the concept of prevention and autism as being aligned with eugenics and other kinds of interventions.

Also concerns that even when we talk about treatment that we may be thinking about that too much in the traditional sense of symptom reduction and not full-functioning.

Part of what the language here represents is an attempt to get past all that as I recall from all of the discussions about crafting this so that we talk about improving the health and well being of every individual on the spectrum meaning that it kind of gets past the whole debate about what we mean by prevention, ethical prevention, treatments, preemption, all those issues, to say what's the ultimate vision here.

It's really not to have simply interventions whether they're early or late but to actually -- at least this was trying to summarize a great deal of discussion that the ultimate vision was improving health and well being through all kinds of different approaches. That's why language that had been in there actually earlier about prevention and

treatment, which does sit at the center of my institute=s strategic plan, doesn't show up here.

MS. SINGER: I think maybe now we've gone too far the other way. I think Stephen actually just proposed a great way to make sure that we are including in the plan what we mean by saying what was your ethical preemption. I understand that preemption is a very sensitive and politically charged word and that --

DR. SHORE: Indeed it is.

MS. SINGER: -- people associate it. That is not what we mean. I think what we have to say very clearly in the plan is what we don't mean and what we do mean.

DR. SHORE: Exactly.

MS. SINGER: I think what we mean in this group when we say preemption is that when we look to do early detection in a genetically predisposed group or any other predisposed population that we want to be able

to intervene either by taking actions or by not taking actions so that we can prevent the onset of clinical symptoms.

I think you know we saw a very interesting example of preemption this week in the media with regard to the one in 500 children who are genetically predisposed to have high cholesterol.

The reporting was really focused on how we would intervene to help those children by changing their exercise regimens by changing their diets and even by intervening medically prior to their showing any symptoms of heart disease in order to preempt the onset of heart disease.

I think that's what we're talking about in this group when we talk about preemption. I think if we state that clearly we can make sure that we're not offending anyone but that we are not losing the important focus on preempting the onset of symptoms.

CHAIRMAN INSEL: Other thoughts, comments? Let me ask you. Given what you just said, Alison, and this really goes with the other comments as well, if the point is clarity, would it make sense to make that one of the cross-cutting themes, that theme of prevention and preemption.

What I am concerned about is, because we spent some time on this last time around the vision and the mission, rather than revising and expanding those as to really lay this out in just the clarity that you just had and to explain what we mean by those terms under cross-cutting.

It's the case that there is nowhere in this overview that we have captured something that the group wanted which was importance of prevention. I guess the question I'm asking is does it need to be in the vision and mission or should we actually put it into the cross-cutting theme.

DR. LANDIS: I think it would

certainly fit as a cross-cutting theme and you can imagine it following on from earlier detection.

MS. SINGER: I also think because we want to make sure that we are explaining what we mean maybe we can mention prevention in the mission statement but further explain because, again, we don't want to be unclear. It may require more explanation than is possible solely in the mission statement so it may make sense to mention it in the mission statement and then expand upon it as a cross-cutting theme.

CHAIRMAN INSEL: My concern about even bringing it into the mission statement or vision statement is because it has been such a charged issue with some parts of the public, some parts of the autism community, I almost don't want to go there until there is the chance to really explain it which is why there may be some value doing it right as a cross-cutting theme.

It was the case not just from one person but from several people who felt that the discussion of prevention needed to be more highlighted in this introductory part.

MS. REDWOOD: But, Tom, I think there is another large section of the community that also feels very strongly that they want to see this disease prevented and they don't want to see any more children or adults suffer with this disease.

I think it's more a miscommunication in terms of how we use the word prevention and that we are trying to prevent all of the hardships that go along with this disease. We are not trying to prevent the person or their personality or their character traits but we want their health restored.

I think there is another very large portion of the community that very strongly wants prevention. I think we can capture both and meet the needs of everybody

on the spectrum.

CHAIRMAN INSEL: So what I'm asking is can we do that with a clear statement that actually unpacks the complexity here in the vision statement or is that something that really would be better as one of the cross-cutting themes?

We have heard, even in these meetings, the last two meetings, from a public comment at the end of the meeting about real concerns on how the medical community will deal with the concept of preventing autism and whether that will be similar to Down Syndrome where 90 percent of the babies are aborted or whether it will be similar to a cardiovascular disease where we use statins and exercise and diet.

That is the kind of complexity I'm sensitive to. I understand there are some people who are really clear on this. I can just tell you that if we are trying to be inclusive and following the values that we

have here and trying to take into account everyone's perspective, I think we have to be sensitive to those people who have a very different perception of this.

DR. SHORE: I think what we're all getting at is that we want people with autism to be healthy, to lead fulfilling and productive lives to the fullest extent possible.

I think what we all want, I guess I can't speak for everybody but I can speak for myself, and that is we are really looking at dealing with the more challenging and debilitating aspects of autism whether it be biomedical, educational, sensory, or otherwise.

You've got a child that hasn't developed a reliable means of communication you've got to do something about that and all we can do about things like that is we go with gusto. The challenge comes in when we get into things bordering eugenics and the

possibility of things like that.

One way to look at autism is an expression of the diversity of the human gene pool. Again, we are also dealing with a number of cases of pretty severe challenges and disabilities that result from autism.

Autism is a different way of being. It's not necessarily a disordered way of being but, at the same time, there are many characteristics that go along with autism that can be debilitating. I think that is what we are all after, working that up.

MR. GROSSMAN: I think that what we're trying to always have is have a sense that people with autism are valued. If we are going to put statements up front that have the potential of being interpreted in a way of devaluing or not valuing individuals with autism that I think it's best to be left in the body of the work that we have to explain it further what we are trying to do.

Prevention is a very, very touchy

subject. We are having this debate here and it shows that there is not full clarity in what its meaning is and if in any way it can be interpreted as devaluing people with autism, then I say that we probably should leave it out because we'll have people rejecting our work just by looking at our values and our mission statement based on what could be perceived as just semantical but it's very important to them.

MS. SINGER: I would suggest then that we include it in the cross-cutting themes where there are about -- I mean, there are paragraphs that explain what each term means. I think the phrase that Stephen used, ethical preemption, I think really should be incorporated because I think it captures exactly what Lee is describing, the fact that we want to make sure that the term preemption is not misunderstood.

I think there is a way for us to do that with language and I think one of the

areas where it is appropriate within the format of this plan is within the cross-cutting themes where language is used to explain what is meant by heterogeneity and what is meant by life span perspective, for example.

CHAIRMAN INSEL: Other comments about this? Alison, you just brought up the heterogeneity issue. That's the other one where there is a wish that we would expand the paragraph to pick up on some of these other themes.

MS. BLACKWELL: I have a comment about the life span perspective cross-cutting theme.

CHAIRMAN INSEL: Right.

MS. BLACKWELL: I think Judith mentioned that this came up several times during the meeting last week. I want to make sure that because we have this as a cross-cutting theme I have a sense that it doesn't always sprinkle down into the particular

objectives and there are ways to address that pretty easily.

In many places again we are talking about children and youth when I think we could use language that is broader that touches on adults as well. I would really be happy if we could adjust some of this language to address everyone with autism. I think that would be great.

CHAIRMAN INSEL: So, Ellen, the way this is worded here, though, because we'll get to the other themes in a moment --

MS. BLACKWELL: Okay.

CHAIRMAN INSEL: -- to answer the questions but for the paragraph on life span perspectives, does this work for you?

MS. BLACKWELL: Yes, it's fine. I just want to make sure that it actually does trickle down.

CHAIRMAN INSEL: We heard this several times in the workgroup so we'll get to that in a moment. What I'm hearing if I can

summarize what we have talked about so far, the idea of strengthening the importance of prevention by putting that as a cross-cutting theme, the sense of urgency which some people felt wasn't obvious enough in the document.

We can make sure that is more explicit if it is only implicit. I thought we had that as actually one of the core values. It's the top core value but if people feel that we need to do more on that, that would be helpful to know. I'm not seeing a lot of enthusiasm for that.

Cutting edge science which, again, in looking at this it is actually the case that there is no place in -- we talk about excellence. We will pursue basic and clinical research of the highest quality to protect the safety and advance the best interest of those affected but we don't talk about innovative science, cutting edge science.

It's not really explicit anywhere. Is that something you would like to see

included? I see a couple of heads shaking. If I see more than three heads shake, I assume that's a yes so we'll go ahead and put that into some part of this introductory section. Early detection I think is there.

Again, that is something that is easy enough as we have already talked about to make sure that we clarify what we mean by that. Story mentioned the value of putting prevention after early detection. Logically that would follow. Heterogeneity, as you --

DR. LANDIS: Actually, that's very interesting because I think the point that Stephen was making was that there are aspects of the autism spectrum which are really disabling and create very significant problems. One would like to actually intervene at that stage to prevent or preempt the further development of those very difficult aspects of the disease or the disorder.

CHAIRMAN INSEL: You know, I think

as this gets -- before this goes out for public comment, on something like this it would probably be good for us to draft -- get the comments you've given us and draft some language. Especially, Stephen, if you'll take a look at it and make sure that it is reflecting what you're telling us.

The last one on here is about greater emphasis on the partnership. Again, some of us thought that was there. It's one of the core values. It's interesting. Several of these things that we listed as core values, urgency, excellence, and partnership, and even the accountability didn't -- when the workgroup read it they kind of missed that. They didn't feel those were emphasized enough. Perhaps one thing we could do would be to frame up that core value section, even just formatting it in such a way that it becomes obvious that these are really key to every part of the plan.

It was really striking in just

looking at this again that things we thought we had covered very clearly they didn't see it. It means that others are not going to see it either so we ought to give some though about how to improve the early detection of those core values.

Anything else from this first section that you would like to make sure that we are changing either because you didn't see it or because the workgroup thought it needed to be changed? Should we go on? Next one.

MS. REDWOOD: Tom?

CHAIRMAN INSEL: Yes.

MS. REDWOOD: I'm wondering if there shouldn't be an additional cross-cutting theme that includes genetics and environment because we clearly have a disease that is not 100 percent genetics, and at best may be 1 percent, and can be explained solely by genetics.

I think that the role of an environment plays such a huge role and that is

a theme that is emerged throughout the workshops, the RFIs. I think one of the cross-cutting themes being the role of genetics and environment together. That gives us an opportunity to focus more on we might not be able to change the genetics but we obviously can work on environmental factors.

I would like to see that or propose that be added as one of the cross-cutting themes as well as the one that we are going to add with regard to describing a little bit better prevention.

CHAIRMAN INSEL: Other thoughts about that? I see heads shaking. Again, this is a place where there might be some advantage of being able to put into a paragraph a complex idea that sometimes gets over simplified.

MS. REDWOOD: With that we could also include the sense of urgency because that does give us an opportunity to intervene in environmental factors so we could maybe put

some of those cross-cutting or core values into that section as well to increase our sense of urgency on focusing on the factors that are truly amenable to prevention.

CHAIRMAN INSEL: Okay. Great. Onwards. So we've got six questions and we've got about 30 minutes we want to get through these. Let's walk through them pretty quickly.

The first one then, around "When should I be concerned?" This is the biomarker early detection piece. Either suggestions you have from just reading it yourself or responses you have to the recommendations of the workgroup. Should we incorporate any of these or just move on?

MS. REDWOOD: I thought the comments were all good. I was wondering if we could get some clarity with regard to the aspirational goal. "All children with ASD will be identified at an early age." Should we decide or put some clarification around

what we mean as an early age. I mean, set a goal for when we really want these children to be diagnosed. It seemed a little fuzzy for me to just have it early age. It wasn't measurable.

MS. BLACKWELL: If we do that, how do we get to people who are diagnosed with autism when they are much, much older? We'll look like we're failing because we didn't get them by age two or age three or age one.

CHAIRMAN INSEL: But that's why it's an aspirational goal. Right?

MS. BLACKWELL: Okay.

CHAIRMAN INSEL: Yvette, did you have a comment?

DR. JANVIER: Working in the trenches in this area I think that would be loaded to say 24 months. That might be very simple for me to do but I think looking across the country, I think that could be extremely challenging so I think you're better to keep it vague.

Some of the 40 goals were to develop a tool that was easy and replicable and effective across a variety of settings. I don't think we're there. I think we need to keep that vagueness. I just don't think it's realistic to say all children in the country will be diagnosed by 24 months. We don't have that capability at this point.

CHAIRMAN INSEL: But if it's an aspirational goal, that is, if this is where you're dreaming and you are looking out into the future and saying, "What could we do?"

DR. LANDIS: I have to say early age. You know, the older I get the younger a five-year-old looks. I think it would be very nice recognizing that people may not be identified but to have some sort of benchmark knowing that you may well not meet it but that you would be driving towards that I think makes sense.

What is the worse thing that happens? You don't need it but at least if

you said it, people will push to do that. Maybe it doesn't have to be all children. Maybe it could be 80 percent of kids would be identified by age. Some more concrete thing. I agree with you that early is very fuzzy. Sorry.

CHAIRMAN INSEL: Other suggestions or comments?

DR. LANDIS: It also would contribute to the sense of urgency. I mean, I know we're not supposed to go back but as I read the sense of urgency, it's a little muzzy and putting something concrete in here would pick up that theme of urgency.

DR. TREVATHAN: Tom, I think while there seems to be agreement that it would be nice to identify all children by 24 months or before, what's currently going on in communities is so far short of that that, I mean, I am concerned about setting a goal that seems so unachievable given the infrastructure and resources that are available in most

communities.

It might be nice to have some statement that it appears that most children with ASD should be identifiable by the age of two or before the age of two and some sort of a goal over the next years we would like to see all children with ASD identified before the age of three or something.

There may be a way to have a statement in there that acknowledges what we think can happen but sort of set what we think is a realistic goal. I guess what that realistic goal is over the next few years is something maybe we should have some folks look into and discuss. I think it would be very nice to have a specific age identified. That is the goal we're shooting for.

DR. LANDIS: And it could be in the research opportunities. It doesn't have to be right up there in the blueprint. It could be down in the research opportunities with some notion of progression over time. By

20 whatever you do X. By 20 whatever plus five you do Y.

DR. TREVATHAN: Exactly.

CHAIRMAN INSEL: So what is the ultimate aspiration if you're doing that? Where are you at Z? Would it make sense -- I guess I'm back on Lyn's point and your sense of urgency.

Would it make sense to say something that was more specific where you would say maybe it is 80 percent by age two or 60 percent. I don't know what the number ought to be but is there a way to give this some teeth so it's not just -- it does look very vague.

DR. JANVIER: I would say that if you're going to put an age, then maybe you need to clarify it and say something -- I know what we're doing is using the tools that are available saying children are at risk for autism. Again, even if we implement the American Academy of Pediatric Standards

screening within M-CHAT, which is not perfect, at 18 and 24 months, you fail an M-CHAT at 24 months and then what's going to happen? Early interventions are not comfortable or willing to identify autism.

It's going to take you six months if you're really lucky, longer to get into a specialist who may or may not feel comfortable giving you a diagnosis but I think with a failed screening classifying a child at risk for autism that is very doable but getting a final diagnosis by age 2 is a lofty goal but, again, without myself sitting at some kind of telecommuting screen all day long and saying, "Yes, yes, yes," I can't see that happening.

DR. HOULE: You could add wording about early identification for children with autism or at risk for autism spectrum disorders. The other thing I would change is that in my opinion I would use received intervention as opposed to care.

I just think intervention connotes

a more proactive way of intervening than caring for someone. You could put a risk factor in there so you are identifying children who may be at risk for ASD.

CHAIRMAN INSEL: So let me clarify. In terms of what we meant by an aspirational goal because it may be that you don't want to have to -- they don't have to be in here. We thought it was useful to set a very high bar. The aspirational goal envisioned for the NCI, the Cancer Institute, is a world without cancer by 2015 or 2050, something like that.

No one seriously believes they are going to meet that but it's trying to hold their feet to the fire and setting a very ambitious goal and a very particular one saying, "This is something we are going to do by a particular date."

The idea of the aspirational goals was to try to do that for ourselves here and to build a sense of urgency but also a sense

of vision and tremendous ambition. I understand the reality. You look at it now and you think this is ridiculous. On the other hand, is there value in putting it in there?

If we are going to put it in there, can we give it some teeth to make it work for us. This is your plan. We don't have to do any of this. It's just up to you on how you want to do it.

DR. JANVIER: I think the aspirational goal then may be to use the implementation of the American Academy of Pediatric Guidelines and state somewhere in the body that 80 percent of children will be screened for signs of autism by 24 months. That is a lot more realistic. Sorry.

MR. GROSSMAN: I think absolutely we need to put aspirational goals in here. The whole purpose of doing a strategic plan is to identify what ain't working and apparently what we are doing for autism in this country

is not working. And to develop a plan that will transform an organization, a community, a society to get to the point where it will begin to adequately address the needs of the community.

I have advocated for this in past meetings that our aspirational goals need to be bold. They need to be strong. Otherwise, we will only go to the point where we will meet a goal. As autism is today we really need to push ourselves. I would advocate strongly that we be as definitive as possible.

We put deadlines in there, a goal of a date, and that we will identify all children with ASD by, for example, age 2 by the year 2012 but that we be as specific as possible. I believe that will also hold our feet to the fire as well as drive the community, the research community, towards trying to achieve that.

MS. REDWOOD: Can I second what he just said? Tom, along those lines I don't

know if you want to get into the specifics of short-term and long-term objectives.

CHAIRMAN INSEL: Yes, this is the chance so any changes you want to make. Again, it doesn't have to be any of these. If there is something you want to change before this goes forward, just point it out.

MS. REDWOOD: Throughout this document I'm just really concerned about the arbitrary nature of how we came up with a number with regard to the things we are going to do. Our short-term goal is develop with existing tools at least one efficient diagnostic instrument. Why can't we develop five? I mean, somewhere in here, I think it's in the area of environment, that within two years we will decide on what areas we need to look at.

CHAIRMAN INSEL: We'll get there but on this one. Let's just stick with this one.

MS. REDWOOD: I just want to see a

lot more throughout the whole thing. I think developing at least one tool I think we should develop several tools. I think we need to -- let's see. We're at 2008 now. Nine, 10, 11. We've got three years to implement those. I guess I would like to see more discussion on maybe adding more to the short-term and long-term objectives.

CHAIRMAN INSEL: On that one about the existing tools, we talked that through with the workshop chairs, the people who are really doing a lot of this work. I remember that exact discussion around how many or what the time frame ought to be for this.

The numbers came from the group and we tend to rely on them because they are the people who do this and know what it requires. Our task is, as you say, to raise the bar and to make this as high-impact as possible. Tell us what you are comfortable with.

Yvette.

DR. JANVIER: I think we need to go back to the discussion we were having. It's boring to have realistic goals. Maybe under the aspirational goal we should say, "Children with autism spectrum disorders will be identified at age 2 and receive care appropriate to diagnosis."

I think, first of all, I mean, some parts of the spectrum you cannot diagnose at two. I think diagnosing at age 2 it is possible in ideal circumstances so if we want it to be lofty, that seems fairly lofty to me.

CHAIRMAN INSEL: Yvette, would you feel better if it said all children at risk?

DR. JANVIER: Well, again, I mean, we could -- I'm just concerned about all because, you know, you could have high-functioning Asperger's, autism, whatever, and you're not picked up at two in the best world. I'm just concerned with how to word that. I'm not really clear but I think at 24 months in the ideal world we should be able to pick

up children with autism, not all forms of ASD.

DR. LANDIS: So I think the hooker in this first short-term objective is this piece of general clinical practice by 2011, I mean, based on what you just said about the AAP guidelines and the complexities of moving something from a research environment into general practice. Maybe it needs to be fractionated with two pieces.

One that you would have it and it would be available in some by X, 2011, and all by Y. I mean, from neurology's standpoint it took 10 years for the notion of TPA for treatment of acute stroke to come into anything remotely resembling regular practice.

The difficulty of moving something from an academic definition into general pediatric practice may just -- maybe we need different timelines for those two things. You might have a different set of tests. One test for general practice would be spectacular, although in tertiary referral centers you

might expect a set of tests.

CHAIRMAN INSEL: That is exactly the discussion that we had.

DR. LANDIS: Sorry I was not here.

CHAIRMAN INSEL: Maybe this didn't get captured so if it isn't clear to you, it may not be clear to anybody else. There were two levels of screening that people wanted. They wanted screening for the general population that would be quick, cheap, and effective but would be not very sensitive but would bring a lot of people -- not very specific but would be very sensitive.

Then they wanted another set of screening instruments, and maybe this isn't in here, that you would use not in the community population but in kind of the next level down and that is where you drill down to get the biomarkers and you do all this other kind of more vertical workup of patients.

This came largely from Cathy Lord who was head of the workshop. When we pushed

her on this she said, "Those are really two very different things and we need them both." We were a little surprised because I think some people felt we had that and she felt that we don't, that current instruments are not very good and need to be replaced.

That is where the 2011 one came from because she said we need to get that out now. That needs to be done quickly but it would take about three years to validate. I remember saying to her, "Why does it take that long? We should be able to do that tomorrow. What's the problem?"

She said to work in diverse populations broad scope validation study is going to take a while because you have to follow the kids to make sure that the instrument is really working. There was quite a bit of thought that went into each of these. What you're seeing is kind of the result of people who are both doing it and people who are trying to understand it.

DR. LANDIS: So the complexity is getting something -- we shouldn=t let perfect be the enemy of good. If this is an organic plan, then it doesn't have to be perfect the first time out of the gate.

CHAIRMAN INSEL: So Lyn's original issue is still on the table about how do you make this even more ambitious and have a greater impact. This was focused largely on that first short-term objective of is it only one? It says at least one so it could be more. Do we need to bump it up to say multiple efficient diagnostic instruments or are you comfortable with having it at least one knowing that it could be more?

DR. TREVATHAN: Tom, I would just suggest that the wording is, I think, appropriate. I mean, I understand Lyn's point. Taking it from the research world into the actual community and clinical world it tends to be much more effective if your general community, general population, highly

sensitive and not so specific screening tool is widely used, easy to use, and there are not too many of them.

That way you can be sure they really penetrate the community well. If we throw 10 to 15 different instruments out there, then it's hard to get wide acceptance. I haven't had this specific conversation with Cathy but I'll listen to that conversation.

I mean, in order to come up with at least one really terrific efficient screening tool and the community may require testing of several to find the best one. At least my memory of the discussion, I think all the things that have been discussed were taken into consideration as you said.

CHAIRMAN INSEL: Duane.

DR. ALEXANDER: As these things are generally crafted, the overall statement like the aspirational goal is often put in more general and generic terms and the specifics put in. What we have here is the

generic concept set forth in the aspirational goal which is at an early age without specifying that age in the goal. Then in the research opportunities or the objectives you can get specific as to goals.

For example, based on a discussion we just had about screening versus diagnostic, you could put it in either the short-term objective or research opportunities a goal of developing an effective screening test for use in infancy or shortly afterwards with a diagnostic test capability by age 24 months, something like that so that you get your specifics not in the overall goal but in the implementation of the goal where the concept is at an early age.

That is much easier to do and much more typical of the way things like this would be done. I don't have a problem honestly with "at an early age" because we don't know specifically here. Plus we are dealing with both the concepts of screening and diagnostic

tools. If we can get that concept in the specific objectives, I think we have achieved what we are really after keeping the generic and overall concept within the aspirational goal.

CHAIRMAN INSEL: That's how the group crafted this, that the aspirational goals would be ambitious but general and that the details would be in the objectives.

DR. ALEXANDER: The objectives here could be clarified by putting ages in. There is not any ages within these concepts.

CHAIRMAN INSEL: For some. The long-term one says accurately identify before age two one or more subtypes. Perhaps we need to look through this and build in more of the ages. We have the time frames but not the ages on this one.

MR. GROSSMAN: Still in the aspirational goals I would want to put some sort of deadline in there in terms of the date just so that, again, it kind of keeps pushing

us to have a goal, to have a defined period over trying to meet these opportunities

DR. ALEXANDER: Date or age?

MR. GROSSMAN: Date. The age part I think -- I'll give on the age part on the aspirational goal but I think on the time frame we should define that better. I also think as I listen to the dialogue that we are getting too technical here in terms of having it defined and a specific diagnosis.

I think in terms of advocacy or families just the identification of something being awry so that we can push these kids towards more specialized services so they can get early intervention is really the primary goal that I think most of us would be excited about.

Most of these kids aren't being diagnosed until they are about four-and-a-half if they're white and upper middle class. If you are a minority and under privileged, it could be as late as six-and-a-half before they

are being diagnosed and that is just precious time that we are wasting.

I think if we aren't as technical as we are trying to be to find an exact screening tool, which I think the specialists can do, but we are putting pressure on those early care or primary care providers, pediatricians to at least identify that something is wrong so they can then refer them on, that will also put pressure on our public systems because I don't think that there has been enough -- that may be my take on this but there hasn't been enough pressure on the public system to respond adequately to the numbers of kids that they are seeing now coming through.

CHAIRMAN INSEL: So I'm mindful of the time. Let's do this. We'll have people work on the parts of this that you have highlighted, the aspirational goals, the short-term objective number one that you were concerned about.

Of the items that are up here, many of these are more wordsmithing or sort of tone and we can -- unless people have reservations about any of them, we'll find a way to work some of those points in, the ones -- actually, some of them are there already but it's a matter of providing a little more emphasis. Is there anything up there that you do not want or anything that you think is really important to include?

MS. BLACKWELL: I have one quick suggestion. I'm okay with early age and I agree with Gail that probably the word intervention is more appropriate than treatment. When I see the word diagnosis I think we might want to talk about people's needs because needs vary and diagnosis could be the same. Maybe it should say, "At an early age and receive intervention appropriate to a person's need."

CHAIRMAN INSEL: Receive appropriate intervention?

MS. BLACKWELL: Yes, or just put the period there. The diagnosis is the diagnosis. The needs could be totally different.

CHAIRMAN INSEL: We can wordsmith it. I wouldn't get too hung up on that. We'll get this back to you before it goes out again. You are giving us the areas that are going to need some additional work. It's going to be very hard to wordsmith it with this many people.

Unless there is anything else from this first one let's move on. Otherwise, this will take us really the entire day. Of the comments that are up anything that you do or do not want to include? Remember you don't have to have any of this in here. This is just for our benefit.

Ellen, this is the piece that you brought up before about bringing in the wide-range of individuals, that we want to get away from the focus on the child.

MS. BLACKWELL: I think by wordsmithing that last long-term objective we can fix that pretty easily.

CHAIRMAN INSEL: Okay.

MS. REDWOOD: Tom, I think those are all great and I hate to keep digging at this but I went through this and have a lot of yellow highlights and comments just about the language and the way it is written. I guess about what we know in that third paragraph when they are talking about some of the immune issues and co-morbidities they say in there, "However, this line of research has not yielded definitive answers to the question of immune involvement."

To me that is a huge opportunity and it is listed as sort of a negative. I would like to see this really sort of rewritten a little differently and I'm wondering if it would be helpful to send comments to you sort of in track change modes.

I think there is a lot of research

and things that are left out in here with regard to things we know now about metabolic disorders and children with autism, oxidative stress, immune abnormalities. That is not really captured in what is written here in regard to what we know. We know a lot more than what is outlined.

CHAIRMAN INSEL: Why don't you send those forward and we'll see how we can incorporate. This was really meant to put some boundaries over what is actually solid. As you can see, all the way through here what is most remarkable is the limitations of our knowledge.

We thought that was important to establish the need to do much, much more. I don't think that we have to make a strong case for having already wrapped up a lot of this. We were trying to emphasize our ignorance more than our accomplishments so far. The next plan will emphasize all the discoveries.

MS. REDWOOD: But it's almost read

as though, "We've tried this and it's not a promising area." That is my read of that one.

CHAIRMAN INSEL: That is very important. That is really what this process is about. That was certainly not what was intended but if you and others read it that way it has to change because that is not what the intention was. It is very helpful to get that feedback so we can make the language more in line with what was intended.

Other comments about this section? Are people comfortable with extending the time frame to 2030 for the long-term objectives?

MS. REDWOOD: Boy, I'm not. That's nuts.

MS. SINGER: If they can cure cancer by 2015, then we can do better than 2030.

CHAIRMAN INSEL: So we will not accept that particular recommendation. Any others up there that you want to just --

DR. ALEXANDER: You can only make kids develop so fast.

CHAIRMAN INSEL: I think, Duane, they were thinking about the National Children's Study with that one but we can do better than 2030. Can't we?

I'll tell you what. Why don't we try to do better and then when we do the annual updates, if we have to we'll end up at 2030. I would like to think that we would start some place a little before than. I don't think any of us will still be on the IACC in 2030.

DR. JANVIER: I had a comment about that also actually because I think we may be doing well in certain arenas but we don't really know when someone is 30 or 40 years old what is the impact of what we're doing and that may be very, very critical with regard to Stephen's earlier discussion.

I often say that to the families I work with that you get through that early

phase and you've got the child talking and they are mainstreamed and they've got normal intelligence but how are they really going to function when they are 20 or 25 or 30? What we have done early on may or may not predict that.

CHAIRMAN INSEL: So that gets to the 6th question about what can we expect long-term. Again, we may not have captured that so we will need to go back and put that in. That is a really important point. We did hear that from the workgroup so we want to make sure that's here.

Anything else from here that you want to include or don't want to include? The idea of the biospecimens, people felt that this was too brain centric and that with the advent of skin fibroblast that can be made into iPS cells, induced pluripotent stem cells, that there were opportunities that they didn't think were being addressed here.

Having a repository of skin

fibroblast, could turn out, in five years could be extremely important, especially when you are trying to define a spectrum and subtypes.

Anything else up here that you think needs to be included? You then brought up the immune and metabolic piece. That could be in the second short-term objective. That could be built in. You want to drop the 2030 and then the aspirational goal idea was to include a wide range of individuals.

Are people okay with that? Ready to move on? If you want to break, we are going to have to move on so we'll make those changes, number three onwards. Again, your comments versus what we got from the workgroup.

One of the big points of contention here, and we did not resolve this in the workgroup, and it also comes up in the letters that are in your package, is the extent to which the plan is specific about

vaccine research and is that going to be discussed either as an objective or as -- well, as one of the objectives under this goal. You can see it up here so we are going to need some direction from the group about that.

We do talk about environmental factors and we don't get -- I don't think we list any individual environmental factors or any individual genes so we have kept it general all the way through but there were some people who wrote in and this also was mentioned about needing to highlight vaccines. Can we get some clarity about that?

MS. REDWOOD: Tom, vaccines were one of the things that were mentioned in both the House and Senate colloquy and it is an important area to the community. I feel strongly that it does need its own separate mention.

There is a growing number of parents who have watched their children

regress after vaccines. I think we are all familiar with Hannah Poling. I think it's on everybody's mind. It's in almost every newspaper today. I think it needs to be addressed.

Cindy Lawler is here. Cindy, at the town hall meeting, the number of parents that mentioned vaccines as being an area that we must investigate?

DR. LAWLER: Yes, it was mentioned frequently.

MS. REDWOOD: And it was mentioned in the RFIs. I think if we ignore that, Tom, we are not being true stewards to really embracing what the public is wanting us to look at. We are ignoring them.

CHAIRMAN INSEL: So I am hearing in terms of the public comments we are hearing both sides of this because there are also comments we've gotten that feel pretty strongly the other way. I think this is one of those places where the IACC has to make a

tough call what you want to do with this item.

DR. LAWLER: What about if we look at short-term objectives. The first one, establish consensus on at least three additional environmental factors. I mean, I think the word additional needs to be clarified and maybe replaced with three or more of the highest priority exposures or classes of exposures.

Vaccines could certainly rise to the top in that sort of forum so that is one way of including vaccines in this plan without having a separate short-term objective.

CHAIRMAN INSEL: So if I can just summarize, the other side of the argument that we're hearing is that a lot has gone into the epidemiological study of vaccines without much to show for it. There is an opportunity cost for taking on a very expensive difficult area.

If you are putting money into that you are not putting money into other things that could be even more likely as

environmental factors. I just want to make sure this is a full consideration of both perspectives.

Story.

DR. LANDIS: So I think what might be interesting, useful, would be an exploration of what you would do to pursue that. What would the studies be like, how much would they cost, and what kinds of answers might you get. So this is very abstract.

Now looking at vaccines but if we actually played out -- I mean, in many of the other kinds of studies and objectives we have a pretty clear notion of exactly what you do, or pretty much what you do and what the cost might be.

The question here is if we were to make it less abstract and more real, what studies would be done, how much would they cost, how long would they take, and what would the answers be if it turns out you can't

design a compelling study. I don't have a dog in this fight so maybe I'm --

MS. REDWOOD: Actually, Tom, you mentioned the epidemiological studies that have been done today. If you read the IOM report they actually say those studies cannot rule out a small subset of the population that might be more vulnerable to vaccine injury and that is exactly what we are saying.

Actually, again, Cindy, you could help with this. Congress asked the National Institute of Environmental Health to look at some of these databases like the VSD database that was used for the Bestatin study and determined whether or not it could answer those questions about vaccines and autism and the response back or the report said no because it's an administrative database.

In that report that came back to Congress, I think it was about eight or 10 pages long, they actually outlined the type of studies that could be done to answer those

questions. I think that has already been determined. I will be glad to share that report that went to Congress.

DR. LANDIS: And do we have any notion of what the cost associated with those studies would be? I think I could imagine myself if I had a choice of an investment in therapeutic development if it turns out it consumes all the resources, or half the resources. I mean, I don't know what the price tags would be.

DR. TREVATHAN: I certainly hear a lot of both sides of this view. I think Lyn well articulates one view, the other being the opportunity cost of continuing to do more vaccine research when it's so far not been very -- it hasn't yielded very much and criticism for us continuing to spend money in that area when every dollar we spend in that area is a dollar we're not spending looking at other options.

There is that tensions between

these two views. Certainly I hear those quite a bit from where I sit. I guess the only thing I would add is that we don't want to forget that certainly the researchers and investigators that are part of our workshops are not vaccine expert researchers. There are separate advisory committees and interagency coordinating committees for vaccine research.

Any efforts such as the one, Story, you're describing which I think knowing what the costs are for developing some of these specific research areas is worth looking into. I would just urge that we need to be aware that isn't the area of expertise to the people in this committee.

Probably it would be worthwhile to connect with those areas that are actually doing the vaccine research agendas and coordinating committee work to really make sure that we are, I think, advising them and they are fully informed of what we're doing and vice versa.

MS. REDWOOD: I can share with you the cost. I hate to say things off the top of my head but like $1 to $3 million.

CHAIRMAN INSEL: We'll get to the cost at a later stage. I think at this point the only real question is how we want to frame this. When we talk about environmental factors do we want to list them or do we want to just keep it general as we have for other parts of the document. As you are hearing, I think there are arguments to be made on either side. I just want to make sure the committee has a chance to weigh in.

Yvette.

DR. JANVIER: I just wanted to say that even though autism may affect New Jersey one of 90 children, the vaccines affect all of our children. It is clearly a challenge for every family, every pediatrician dealing with these questions.

Certainly there is very good research out there to show that there may not

be a link but I think the media or other organizations are promoting looking at other concerns. I think we do need to address it somehow.

I don't know if it's possible for us to have -- you know, I think the American Academy of Pediatrics and the CDC people are kind of poo-pooing that. It's like, "Oh, well CDC is hooked in with vaccine companies." Or, "Pediatricians make money on vaccines." That is just being kind of down played but maybe there's a way.

You can put wording to include vaccines but I think it's a national health concern that children are not going to be vaccinated because of the scare. I'm not sure where this committee could play a role with regard to leadership and getting information that is already been collected out there to support ongoing vaccines.

Again, I think that the pediatricians are not being heard. They are

running scared. They are being intimidated by families to do things that are not what they should be doing. It's really a problem.

CHAIRMAN INSEL: I guess one thing that the committee would have to consider is whether singling out one particular factor would be read as endorsing that as a real probability or whether there is a way -- should we list many things as possibilities.

We can go back to the IOM report on the environment where there were two or three days of discussion about what are the things that are most likely that we should be looking at. If people feel there needs to be some granularity to this, we can do it.

I guess I'm not getting a clear sense of what the up sides and down sides would be of going into this. I am hearing that to not talk about it would be conspicuous in some way. If it's a major issue and the IACC or the document doesn't address it, then you have to ask where were we. Were we asleep

at the wheel?

At the same time if we single this out as the environmental factor that we want to study, does it say to the community that we think this is the smoking gun that just has to be identified.

That wasn't the take-home from the IOM meeting on the environment which was there was a whole range of things that needed to be evaluated. Some of them prenatal and some of them early postnatal. There was a whole panel that needed to be considered. Vaccines were actually, as I recall, not high up on that list.

DR. VAN DYCK: I think under the short-term objective the suggestion was made to establish consensus on at least three additional environmental factors. I think you can then say "such as" and list five or six or seven from the IOM report which would include vaccine research.

There you have not missed it and

overlooked it but you have included it in one of those items that you could establish and you have to work on establishing consensus around. That might be one way of approaching it.

CHAIRMAN INSEL: Other thoughts? I see heads nodding all around. We can have the team go back to the IOM report and pull some things out.

Christine? Okay. Duane.

DR. ALEXANDER: I was just going to say I can certainly understand the concern about if this is being a document that reflects a lot of public input. Being silent on the issue of vaccines is a potential real problem. I also understand and respect the fact that the scientific evidence just isn't there at the present time.

A possible approach to recognize the concern but not jump in and recommend a big research program on it would be to say something like one of the things we should do

would be to monitor the issues of the possible association of vaccines with ASDs and identify needs and opportunities that emerge for research and implement indicated studies, something like that so that you continue to monitor it, you look for needs and opportunities for research, but you don't commit yourself to a major research activity unless something comes up.

That is a way of indicating, I think, that you recognize the concern, that you're not convinced that there is anything imminent and immediate that has to be done. You're monitoring it and in case something does come up, you are ready to jump in. That is one approach.

DR. TREVATHAN: I would just -- Duane's idea sounds really good. I would just emphasize, though, I would think that Peter's idea of having a list that is not certainly comprehensive would be helpful because we certainly don't want to give the impression

that environment is just a code word for vaccines.

If we do vaccine research, which again there are other committees advising on that, that we have then satisfied our need to do environmental -- look at environmental exposures because we certainly believe there are other very important environmental exposures. We don't want to downplay them or interpret it as down-playing them by not listening them specifically. The wording, I think, will be important.

CHAIRMAN INSEL: Okay. So we'll come back to you with rewording of that which has some granularity to it, not limited to one particular factor. We may end up doing the same thing on the genetic side because, again, we haven't been granular there either although there are lots of interesting candidates. I think there's a way we can fill this out a little bit more.

I'm very concerned about the time

at this point so let's look at the rest of this. Is there anything else? Let's go back. The cellular high throughput systems was the idea of using iPS cells that can be built in some place. That is the same as the cell lines from individuals with ASD which would have the same impact. The concept there was to use cell lines to actually do screening instead of just doing toxicology.

DR. ALEXANDER: I think that would be a valuable addition.

CHAIRMAN INSEL: And then the worry about preemption, Alison. This is the concern you had. We'll deal with that earlier on in the document.

MS. SINGER: Okay.

CHAIRMAN INSEL: It's very helpful to get this explained. Let's move on very quickly. I've already robbed you of your break.

MR. GROSSMAN: On that goal can we add recovery to that where it says prevention?

We are going to deal with the word preemption. I don't want to say replace preemption with this term but to add recovery.

CHAIRMAN INSEL: Meaning when we do this as a cross-cutting theme? So in that paragraph?

MR. GROSSMAN: Yes.

CHAIRMAN INSEL: Okay.

DR. HANN: Or do you mean the aspirational goal itself?

MR. GROSSMAN: Aspirational goal.

DR. HANN: Would the word recovery added to that so it says "preemption, prevention, and recovery."

MR. GROSSMAN: The preemption one I guess there is still some discussion if that is going to be included but the prevention and also recovery.

CHAIRMAN INSEL: Great. Okay. Great idea.

MS. REDWOOD: Tom, I feel like this is so important and we are really rushing

through it. I mean, this is what we've been talking about for the last several months and I'm concerned that we're really not allowing enough time to go through this document.

CHAIRMAN INSEL: We're not finished.

MS. REDWOOD: I know but there are just things that I feel like we are sort of rushing through and there's still a lot more discussion that needs to take place.

CHAIRMAN INSEL: So is there anything else on this question 3 that you want to make sure is either put in or taken out? On the text for what do we know, what do we need, you'll send us highlighted comments, tracks comments, and we can try to incorporate those.

I'm more concerned about the piece on the objectives because that's where -- that's the next big phase of this and we need to get the objectives at a place where everybody wants them.

MS. REDWOOD: Establish consensus on at least three additional environmental factors as targets for study as potential causes by 2010. Can't we sort of establish a consensus now based on the IOM report? That just seems like it's going to take us two years just to decide on what we want to look at. That's just not -- it doesn't give us a sense of urgency.

DR. LAWLER: I agree we can do that piece more quickly. In my earlier comment, again, it doesn't have to be new or additional environmental factors. In many cases there is a little bit of provocative data and the highest priority is to conduct a more thorough, systematic study. I think, again, the consensus is on prioritizing the classes of exposures or individual exposures.

I also had a comment. The third short-term objective is just too general so that really needs some work. I'm not sure where it came from whether it was an attempt

to try to apply some of the cutting edge technology development in exposure assessment to autism or --

CHAIRMAN INSEL: I think from the discussion this was whole genome epigenomics in cell lines from individuals. Again, if it's not clear to you, we can spell it out. We can make sure the language is -- we can give examples of where the cutting edge technologies are now for identifying gene-environment interactions and epigenomic tags, that kind of thing. And how to get the right cell-based systems for that.

Lyn is bringing up, I think, a really critical issue here. The first short-term objective is pretty general. What is the opposite of ambitious? It's pretty modest in terms of its reach. Is that okay?

DR. LANDIS: If there is an IOM report from which one could select three additional factors for study, it's July. Maybe we could do it early in 2009.

DR. LAWLER: I don't think there was a consensus from that meeting about what the highest priority ones are.

DR. LANDIS: You are talking about three as targets for future study. Either you need to sharpen up what it is you're going to do with them or you need to push it earlier. I mean, you could even -- that is so general as to what you do with it. You could just put them in a hat and almost pick them out.

CHAIRMAN INSEL: So, Story, you would say if establishing the consensus is the goal let's do that right away. Right? Then the long-term objective could maybe be a little more short-term. The first long-term objective is to determine the effect of two additional factors. Is that where we're going here? It does seem it would take two years to decide on what you want to do.

MR. GROSSMAN: I'm struggling here. I don't know what we are saying. Additional to what?

CHAIRMAN INSEL: Yes, additional is gone.

MR. GROSSMAN: Okay. Additional is gone. I say we choose the highest priorities, whatever that is, not make it number-specific.

MS. REDWOOD: Tom, could I also suggest under research opportunities that to me, one of the things that we really continually overlook is actually testing children with autism to see what they have in their bodies. I mean, I get reports all the time from parents where children are just dumping out aluminum, mercury, lead, cadmium. There is testing you can do for PCBs and body burdens. We have this wonderful, rich NHANES database of what is in an average American.

I think if we want to really take this translational approach and go from bed to bench, why don't we test the children with autism to see what is in them and then maybe that will help us to identify what chemicals

should be priority to understand better what they do in the bodies. We don't even know what's there. Am I being overly simplistic here?

CHAIRMAN INSEL: I don't think so, but clearly then you wouldn't see the third research opportunity including that, so standardizing the methods for collecting and storing biospecimens. You're talking about something beyond that so I'm just trying to see if it's in there.

MS. REDWOOD: I'm just talking about testing children now. Maybe even just using the NHANES protocol of 132 environmental toxicants to see what is in there.

CHAIRMAN INSEL: The last opportunity doesn't include that under research opportunities, efficient and accurate measures of biomarkers and environmental factors.

Lyn, what you're asking for is probably one of the objectives. Right? It

looks like it so --

MS. REDWOOD: I just think this area still needs a lot more work.

CHAIRMAN INSEL: Yes.

DR. ALEXANDER: Perhaps a way of dealing with the timing and date question in the first of the short-term objectives would be to say that what we ought to do is do this study of potential causes and initiate studies by 2010. It shouldn't take us that long to reach consensus on what we are going to study. We should be able to initiate the studies by 2010.

CHAIRMAN INSEL: I see heads nodding on that.

Della, you're capturing all this. Lyn's issue is also about doing studies of either exposures or -- I'm not sure if that third short-term objective by 2011 to validate at least three measures for identifying markers in environment and biospecimens. That doesn't do it, or does it? If it isn't clear

to you, it's not going to be clear to anybody else.

This is going to need some additional work. Again, let's highlight this one. It's one that we'll have to clarify with your help and we'll come up with some language that does the kinds of things you're talking about. That was in the discussion. People wanted it and if it's being left out, it's probably because the language doesn't reflect the discussion.

MS. REDWOOD: The language seems really vague and it seems to me that we already have ability to measure these things in biospecimens so I don't know why and I would really like some help from NIEHS with regard to what we can accurately measure and not measure. Maybe Cindy could get together and flush this out some.

CHAIRMAN INSEL: Okay. We were hearing in the workshop that, yeas, we can do some of this but there is no standardized

protocols and that is part of why there is no reliability in the literature that's out there and there is no credibility for much of it because you can take the same specimen and send it to five different labs and get five very different results.

I think what the workshop and what other people have been asking us for is to develop some standards that will provide much more credibility in this area. What might be good is to actually be a little more granular here and say where do we need it most of all.

What are the measures that we really need to focus on. What are the technologies that we need to bring to bear here. Is it mass spec? Is it a new set of ELIZAs? What can we do that will really make this work so that we get past the impediment that we're facing right now.

How are we doing as a group? Do you want to take a break or do you want to keep going on this? We've got to get this

done. This is our document and we can't send it to somebody else to approve. Are you good for a little while longer? The last one is pretty simple. I think it's the next two that are going to require more time. Keep going? Okay.

Question 4. Your reaction to the workgroup comments. The last one, again, Ellen, is your point and so the workgroup felt that needed to be incorporated. I think we are hearing that from the group here as well.

MS. BLACKWELL: I actually think that would be pretty easy to do just by altering some of the language in the short-term and long-term objectives.

CHAIRMAN INSEL: Okay.

MS. BLACKWELL: I didn't understand -- there are a couple places in here where we are looking at siblings of children and I wasn't sure why we were just looking at siblings of children. Why aren't we looking at siblings period. Also there are

places like, launch 3 randomized control trials of interventions of school age or adolescents. Right there is a place to add the word adults.

Then the last short-term objective, again, I'm not sure we want to talk about it. I mean, why are we just looking at early intervention control trials? Why not look at families that include a person with autism? That seems like a really -- this is a place where it just seems like we can integrate adults.

CHAIRMAN INSEL: I didn't understand. So you were thinking early intervention means early in infancy. Right?

MS. BLACKWELL: Well, can we not look at intervention for adults as well as children and how it impacts the family?

CHAIRMAN INSEL: We can do whatever you want. What is down here is what we heard from the workshop that dealt with this.

MS. REDWOOD: Tom, with regard to research opportunities, we had also talked at the workshop about studying recovered children and looking at their histories and see if we could tease out potential risk factors or things that were successful for that child. I think there is a wealth of information available in studying documented cases of recovery.

CHAIRMAN INSEL: So that was the first objective. Again, if this doesn't sing to you, it's not worded right. It was just in response to that point. Interesting that I read this the first time and didn't make the connection either so I thought it was just my misread but that is what that first short-term objective is supposed to identify.

MS. REDWOOD: It's not clear to me that we are looking at recovered children.

CHAIRMAN INSEL: Okay. I'm not alone. Okay. Good.

MS. REDWOOD: We had also talked

about doing studies of one, n of 1, and doing multiple baselines with interventions. I don't see that reflected in here either.

CHAIRMAN INSEL: The workgroup felt that we also didn't have enough emphasis on, as they say it -- where is it? -- current wide use. Yes, study of treatments in current wide use by parents and families. They didn't see that in here. It is in here but apparently it wasn't evident or wasn't emphasized enough. We were going to try to clarify that was also in the objectives along with the n of 1 studies.

The third piece up there which was the kind of personalized approach of what works best for which individuals, again we heard that from the workshop. We thought that was in the language but, if not, it is something if you agree we should build in here. Given the heterogeneity, this has got to be a really critical piece, because then it=s not going to be one intervention for

everybody.

Anything else from the interventions piece here? Okay. Again, you'll get this again before we put it out so you can see what the revisions look like. Let's go on to services.

MS. REDWOOD: Tom, short-term and long-term objectives. I just would love to see a lot more support for your randomized case control trials addressing co-occurring medical conditions. Why can't we do five or ten? Where did the number three come from? I guess I just want us to be more ambitious.

We have a disease that is costing $35 billion a year and we are going to do three studies on treatment which is a huge area that has been under-funded in the past. I would really like to see these short-term and long-term objectives much broader, much more --

CHAIRMAN INSEL: Ambitious?

MS. REDWOOD: Yes. Thank you.

DR. LANDIS: I'm sorry. I agree with you on most of these. Just in Parkinson's disease we have been driven to do trial switch -- come out with really good priority scores but probably don't make any sense biologically so the question is if you set the bar for a large number, are you going to engage parents and families and kids in trials which may not have any real hope of doing anything positive.

I mean, I am obviously not the right person to make that judgement. I'm just speaking from my experience with a different disease where we learn from experience that you can run trials and engage patients and at the end it is a futile trial and then you look back and say, actually, if I had been a bit more discerning when we started, I would have known it wasn't going work.

MS. REDWOOD: Story, I agree with you 100 percent. I think one of the problems we've made is we have tried to take an

intervention and apply it to all children with autism without actually looking to see if there is an abnormality there.

For example, administering methyl B-12. We didn't check first to see whether or not the children had elevated methylmalonic acids or a functional B-12 deficiency. Obviously it's not going to be beneficial if the child doesn't have a B-12 deficiency.

The ones that respond favorably just wash out the ones that didn't so we need to actually identify these abnormalities and then focus on targeted treatments and see if they are effective.

DR. LANDIS: It's kind of like Parkinson's, it=s not just one disease.

MS. REDWOOD: And that's because we have not really recognized the heterogeneity and focused our clinical efforts on this specific identified abnormalities. I agree with you.

CHAIRMAN INSEL: So what if we

were to say, support at least three of Story's reservations without putting a high number. That means that at least for an objective as opposed to an aspirational goal that you could be forced into doing something that you really don't want to do but at least set a floor if not a bar.

MS. REDWOOD: I could think of 10 things right now that parents are doing that we could investigate and help provide some guidance because right now they are shooting in a black box trying these things.

CHAIRMAN INSEL: But this would allow us to do 10. I think if you want to put a number here, it's got to be a number that everybody feels comfortable with. I'm looking for your comfort zone. If the number were 10, do people feel okay about that? Nobody wants it to be one so if we say at least three, is that something that people can live with?

Story? Use a mic.

DR. LANDIS: Given what you've

said, it is a little like spinal muscular atrophy in that regard. The parents are trying a whole lot of different things. The question is, is there any mechanism by which you could assess those in a way that would allow you to say futile/non-futile before engaging in a large Phase III clinical trial to sort through what are the most promising.

MS. REDWOOD: I think that is where your biomarkers come in.

DR. LANDIS: I think you need to get people to say, how many are happy with at least three? How many are happy with five? How many are happy with --

CHAIRMAN INSEL: So, language. We need to move on. Story has a recommendation. At least three versus five versus at least five. At least three. How many people want to go that way? At least five? Hands are up. Okay. At least 10? Okay. At least five.

We are moving on to question 4. I'm sorry, question 5, services. Azik, thank

you. These are the comments from the workgroup.

DR. LANDIS: I have a question about reimbursement. It's pretty clear whether or not something happens depends in part on whether or not there is adequate reimbursement for that. If you go back to the issue of identifying children early who are at high risk for autism, would that be at a well-baby visit in a pediatrician's office?

My recollection from 30 years ago when reimbursements were probably a little better is that the well-baby visit takes about five minutes of contact with a parent and the child. Does there need to be some assessment of changes in reimbursement that would give the pediatrician another five minutes with the child and the family to actually do this like a cost-benefit ratio?

DR. JANVIER: That's been done. I mean, there is a code for developmental screening and there is reimbursement attached

to that code. I know I'm involved in a project in New Jersey implementing the guidelines so basically training the office staff to complete the forms, look for early signs, provide resources, and so on.

I think that piece of it has been -- is in place. It is not a huge amount of money but you can have an office staff have a parent fill out a questionnaire, score it, and put it in your chart when you see the child.

DR. LANDIS: And to the extent that reimbursements are focused -- are more generous for procedures rather than --

CHAIRMAN INSEL: Can I move this on because I'm concerned again that we're going to get into too many of the weeds here.

DR. LANDIS: Sorry.

CHAIRMAN INSEL: On this particular item when the workgroup started to jump into it, they felt that it needed a fair amount of conceptualizing, particularly the section on what do we know was just

misdirected and that there is a whole set of research on the prevalence of services rather than the prevalence of autism.

That is what should be described here. It wasn't simply one person who felt that. There were many people in the workgroup who said, you need to look at this and reconsider how you put this together.

The same with the aspirational goal and with these objectives. There were people on the workgroup who were deep into this area and felt that we needed to rethink a little bit how we had put this together. Are you comfortable with those suggestions?

Some of us who listened in to the discussion thought that was a very thoughtful and more informed discussion than we had had when we just got together with the workshop chairs and a few other people. So I think the team had hoped to be able to incorporate all of this in pretty much the language you see up here. Okay?

MS. BLACKWELL: The only other addition I have is in the paragraph called, what do we need, I'm kind of mystified by the missing word under -- when you talk about funding the word federal is missing here so we need to acknowledge that the federal government does contribute to funding for services. Thank you, Azik.

CHAIRMAN INSEL: Della, do you see that point?

DR. HANN: Yes.

MS. BLACKWELL: Story brought it up. I mean, it says here -- there is a sentence that says, care for developmental disorders is financed largely by state and local agencies.

CHAIRMAN INSEL: Oh, right.

MS. BLACKWELL: Okay. It should say federal comma state. Thank you.

CHAIRMAN INSEL: Anything else from question 5?

DR. LANDIS: To perseverate, just

the issue of setting appropriate reimbursement levels, which is a federal issue.

CHAIRMAN INSEL: Lee.

MR. GROSSMAN: I'm sure this is too much to ask but at the end of the aspirational goal we could add the word today, which would be a big wish.

CHAIRMAN INSEL: I missed that. What was it?

MR. GROSSMAN: To add a word at the end of aspirational goal that, communities will implement high-quality, evidence-based and cost-effective ASD services across the lifespan. I added the word today.

CHAIRMAN INSEL: With an exclamation mark.

MR. GROSSMAN: With an exclamation point.

CHAIRMAN INSEL: Okay.

MS. BLACKWELL: I have one quick thing under short-term objectives, the second one. I wasn't quite sure and maybe,

Tom, you can explain why we are going to be looking at how variation and access to services during the diagnostic process affects family functioning. Wouldn't we want to look at how access to services impacts family functioning period, not just when one individual is being diagnosed.

CHAIRMAN INSEL: Judith or anybody have any memory of how that got there? Della?

DR. HANN: I think, actually, it happened. This was discussed in more than one group at the workshop and it actually was discussed in the detection and diagnostic workshops as something about, how does the fact of going through that process and finding out that your child is at risk or that your child is being diagnosed with one of these disorders impact back on the family and then their search essentially to try to find adequate services.

I think it was a blending, Ellen, and I think the workgroup that met last week

also identified that should be expanded. I believe that is up there but it shouldn't be focused just on the diagnostic process but it should be expanded out.

CHAIRMAN INSEL: So that's your point, Ellen. Right?

MS. BLACKWELL: Yes. I mean, it could be an adult being diagnosed with autism whose family members were impacted.

CHAIRMAN INSEL: That is what they felt in the workgroup is that second objective needed to be -- they were talking about the long-term objectives, not the short-term.

MS. BLACKWELL: To me this is more than understanding what it looks like when a person is diagnosed. It is understanding how access to services impacts what is happening to the family.

CHAIRMAN INSEL: Right.

MS. BLACKWELL: That is a much broader goal.

CHAIRMAN INSEL: I think what you

are looking at is a bad marriage between two good ideas. They started off in the right place but they never merged in the right way so we'll work that up. That needs to be changed. Even the wording doesn't sound right. It's hard to know what this means. Anything else on question 5?

(No audible response.)

Question 6. Here there wasn't as much from the workgroup. These two elements that they wanted us to consider. This was the one that came up earlier in the discussion today about a long-term objective to study the long-term effects of intervention programs on adulthood.

Ellen, I think you were the one who was saying that maybe it shouldn't be just early intervention, but interventions of any sort. Somebody was bringing that up, to look at long-term impact.

MS. BLACKWELL: I didn't understand when I looked at this aspirational

goal, advances in intervention and public understanding, I wasn't quite sure. What are we trying to get to with that? How do we make the public understand and what do we want them to understand? I just didn't understand why that was in there.

Then when we talk about research opportunities I think we need to -- I don't understand why we are looking at longitudinal studies of both children with ASD and their families. To me it should be people with ASD and their families and then following the larger trajectory. That seems to be more consistent with this last question.

The only other comment I had is that when you talk about -- I was happy to see this mention at the top of page 21 about adults with ASD that are involved with the criminal justice system. I think we talked in some of the workgroups about oral health. I'm wondering if it wouldn't be useful to at least bring it up here because it is a special issue

for adults with ASD. I don't know why we just put the criminal justice system in here.

CHAIRMAN INSEL: Comments? Does anyone want to comment on Ellen's suggestion?

DR. TREVATHAN: Well, my memory of the issue of public understanding is that the discussion was along the lines of how much of the public does not understand that many people with autistic spectrum disorders can live full lives and have much to contribute to society.

We obviously, and I think appropriately so, focus on discussions of people who are very severely affected. At the same time, we don't want to short-change people who really are out there, that the public needs to be aware of their ability to make great contributions.

I think there was some discussion actually, whether it was directly stated. There were concerns of discrimination against people with autism making sure that that

wasn't a problem. There was a public education, public awareness understanding need in that area.

I don't know, Lee, if you would agree.

MR. GROSSMAN: In the disability community there is a big distinction between understanding and acceptance. As much as I would like to see acceptance in here, I'm not sure how you would dictate that in a goal whether the public accepts it. I would also like to see the public understanding change a little bit to be more reflective of acceptance but, again, the full understanding that is not something you can really dictate.

DR. SHORE: I think there is an important distinction between the two, understanding and acceptance of autism. Again, there is a different way of being. Not necessarily disordered but there are many things that are disordering about autism and that's what we're all here for.

CHAIRMAN INSEL: Any other suggestions for this last bullet, the last question?

Christine.

MS. McKEE: Under what we know we talk about supporting these individuals to lead healthy and meaningful lives. We've had discussions before about meaningful. Maybe the word fulfilling instead of indicating that there is a life that is not meaningful if we don't intervene. Anyway, I would just like to wordsmith that.

CHAIRMAN INSEL: Okay. Thanks. All right. Let's do this. This is hard work and it's impossible to get this many people to finish a document like this so the team will take all the comments you've reviewed, all the comments that you've added. We'll rework this document, get it out to you fairly quickly.

We need a vote on this but I can't ask you to vote on something that is in this shape because there are going to be so many

changes to it. What I think may be best to do is to have an electronic vote once we can get this distributed with all of the changes. If we do an electronic vote, we need to make the vote results public in some way so your vote could end up being identified so you need to be aware of that.

We'll try to do this over the course of the next several days. As much as this has taken a long time to discuss it, actually some of these changes are more changes in tone and wording and I think we can make this a much better document with all of these kinds of inputs. We'll try to get this to you fairly quickly.

I'm not going to ask Della to put a date on that but it will certainly be before 2030 or whatever that date was that was up on the screen. At that point, if we have a sufficient support for this, that means a majority vote, we will put this thing out for public comment.

Everything is going to come back again with public comment and it will come back, as you will hear with the next session, with budgetary requirements and a bunch of other things that are not in this document for you to look at in November and that will be really where the rubber meets the road.

That will be the document that we are going to need your final approval on that will then go to the secretary. We would like to have it there by Thanksgiving. It's going to be very important to get this done by November since we'll have a change of administration and there is a lot of concern about what could get lost in the transition so we want to make sure this is completed November 21st.

We are almost an hour, or over an hour behind schedule. Lyn.

MS. REDWOOD: I just have a quick question. Can we have at least a week to get back with Della with some more information

regarding the areas that are identified as what we know and what we need to know?

CHAIRMAN INSEL: I don't think you are going to get a finished -- you are not going to get a revised document within a week so if you want to do it over the next week, that would be great. If we could get your comments, that would be very helpful.

MS. REDWOOD: Okay. Thanks.

CHAIRMAN INSEL: And anything else that wasn't captured here that you think is really going to be important to improve the plan, let us know, remembering that there will be another wave still coming after we have the public comment.

I'm sort of inclined to just push on through and then take a break at lunch because we are so far behind schedule. Is that okay? We have one other fairly complex issue that we need to deal with which is the next iteration of this plan and where do we go from here. Everybody okay with hanging in

there for about another 35 minutes? Okay.

Della, are you going to take us through this?

DR. HANN: Yes.

CHAIRMAN INSEL: Okay. This is now the next steps for the plan.

DR. HANN: Okay. I will try to do this as efficiently as possible, knowing that many of you probably have biological needs that you would like to attend to. With that said, I also first wanted to let you know that there are a number of new additions that have been put on the IACC website.

A lot of information was posted over the past week actually with regard to the strategic planning process that we've been going through and a number of documents and summaries are now available on the web.

So what I would like to go through are a variety of topics with you, all of which are for your consideration. None of this should be viewed as *fait accompli* by any means

but to discuss with you various options for how the committee wants to proceed with public comments on the draft plan.

Then how the committee would like to proceed with regard to helping to develop budgetary requirements. One of the ways that we thought of doing that would be to potentially form another workgroup to have that task and obviously bring that back and report to you all about that. And then just to remind everybody sort of what the timelines look like with regard to this.

The first options are the ones with regard to the public comment phase. As we just talked about, we anticipate if we can have your input within a week's time, then hopefully within a week's time we can have another draft out to you for determination if you think it's ready for public comment.

We can do this in a variety of ways but the key part to remember, too, is the timeline pieces of it so we really would

anticipate that if we are able to put a draft out for public comment by the end of the month we would be looking to obtain most of that public comment between that period of time and the end of September so that we have sufficient time to take that comment and then reintegrate it back into the draft.

One way of doing that is through the RFI process -- which this group is familiar with since we did it at the launch essentially. The plan was launched through an RFI process -- requesting information and asking people to comment on the plan. That can be done fairly quickly once you all approve the plan for public comment.

Other means that this group has used in the past for various other functions has to do with convening town hall meetings and possibly webinars. Then another idea that is possible for you to consider are doing smaller groups as opposed to a town hall meeting, which tends to be a bit more formal

and also large. The idea would be to try to convene smaller groups which we are calling focus groups but smaller groups of folks to come together and discuss aspects of the plan.

The key for all of these different methodologies, whichever ones you all choose or combinations that you choose, is the input will be summarized and that summarized information or, if it's the RFI, the actual incoming responses, will become public.

They will be posted on the IACC website and people would know that when they are submitting their information that it would become public. We would be going through that information to identify themes and look for issues of clarification in order to revise the draft yet again. So that's the public comment phase of it. Are there any questions or topics that you would like to raise?

MS. BLACKWELL: Do you want us to talk about which ones we think might be optimal, Della?

DR. HANN: I think that would be lovely.

MS. BLACKWELL: Okay. I personally am a big fan of the RFI response because I think it gives everybody a chance to weigh in. I mean, when we have town hall meetings for everybody it's not a convenient time. The same thing with the webinar. Not everybody has a computer. Focus groups involve certain geographic areas. I think the RFI approach is really optimal to get the most public input.

DR. HOULE: I would concur with Ellen totally.

DR. HANN: All right. Well, we're not done with this by any means but I can move on now to the next part which is the implementation area. After that we can have complete voting essentially on all the different methods and things that you all would like to do.

Implementation workgroup. The

idea here is to form a workgroup. Again, you all have experience with forming the workgroups. The task of that group, which I'm actually going to go through more formally in the next slide, is to make recommendations about how the plan will actually be implemented. It would include the budgetary requirements element that is a requirement within the act itself.

In thinking that through, it seemed logical that this group would be comprised of organizations that are funding research. Since those are the people who are implementing the plan, really, in terms of putting dollars to different sections of the plan, that's who would be responsible for doing that type of work.

This group, we would like again, to move as quickly as possible so that this workgroup will be convened while we are getting the public input. For example, one scenario would be that we would put out the

RFI at the end of the month.

The RFI would be out for 60 to 90 days, whatever the time period is that you all feel comfortable with. During that period of time, say in August, this workgroup would meet in order to start formulating its recommendations.

Charge of the workgroup. I think foremost there are three major pieces to it. One is the budgetary requirements piece which is articulated within the law. The second has to do with issues of accountability which harkens back to the values of this group and the idea that we really want to know who is going to be responsible for actually making sure that the plan is carried forward.

Along with that are issues of having milestones for progress. How will we know that we are actually making progress in some of those initiatives and objectives. And the time frames. Granted, we were just talking about the year time frames but when

one sits down and starts to really think it through a little bit might there be other kinds of milestones and time frames one wishes to establish?

Along with that and also that was recommended through the workgroup process was consideration of the various types of funding tools that the different agencies and groups and organization have at their disposal. I put two here but there are many others. Grants contracts are sort of what come to mind but there are others that can also be used as well as methods of peer review.

There have been comments in several forums now about the fact that we want to have rigorous and strong peer review. Yet, at the same time, we want to make efforts to inspire innovation and risk-taking and we may want to, therefore, consider alternatives or ways of stylizing peer review in order to foster that more innovative and risk-taking kind of thing.

Then the last issue having gone through all of this has to do with the meeting format. Because this group will be talking about potential funding issues and how they may or may not be spending their money, it's probably important that that conversation be held so that people who would actually be responding to those research initiatives, the research community, etc., not be involved because it would give them unfair advantage and we wouldn't want to do that.

We wouldn't want to have a class of haves and have-nots in terms of having prior notice that something was going to happen. In that context it may be worthwhile to consider having this particular workgroup meet in a closed forum. Obviously the proceeds of that meeting would be brought forward to this more public --

Potential organizations to consider. By no means is this definitive. This was brainstorming on our part to try to

think of the variety of organizations as well as different sectors within the federal government that are involved.

NIH and CDC is sort of a given but you'll see two we've listed. HRSA because of the vast resources that HRSA now has that may be important for infrastructure purposes in terms of getting some of these aspects of the plan completed.

Ellen, because of the recent work that you're launching, too, with your RFP for services that it would be important to consider having you there as well.

MS. BLACKWELL: I'm wondering why Gail isn't up there.

DR. HANN: This was brainstorming. By no means was this to be viewed as definitive.

Finally this is a cartoon to help dramatize, if you will, the timeline for the plan. I think the other thing that this dramatizes is the amount of work that you all

have put into it to date. A great deal has been accomplished and I think everyone should feel very good about that.

As you can see with the lighter green elements here, we are anticipating being able to accomplish the public comment in August/September as well as convene or develop those implementation suggestions vis-a-vis the workgroup.

That would occur hopefully in August or potentially early September -- but I know early September often is a very tricky period of people's lives to get things done -- such that a final draft can be submitted to you for the November meeting consideration.

And that's what I have.

CHAIRMAN INSEL: The big issues here are who will serve on the implementation workgroup and what the charge for the workgroup would be. We are going to need your input about those issues.

MS. BLACKWELL: When you had that

slide up showing the folks that you thought should be on the workgroup, you mentioned you thought of a person with ASD or people with ASD?

DR. HANN: That is correct.

MS. BLACKWELL: I wondered why a family member of a person or persons with ASD wouldn't also be included.

DR. HANN: Yes.

MS. REDWOOD: Tom, I'm just wondering. It seems like we have gone through this process several times of creating workgroups and we have a very strong workgroup now which actually IACC personally selected.

I think they are intimately familiar with this plan and I think we have resources there already that can do these next steps with regard to budget requirements and all the things you've outlined. I would have to call the question of whether or not we could just supplement the group that we have already versus starting all over again with a

new implementation workgroup.

DR. LANDIS: So I think that part of that implementation committee is going to end up coming up with strategies for implementation, although maybe I'm wrong about this. RFAs and program announcements and RFPs, at least for the federal government piece of it, there are pretty strong regulations about exactly the kind of thing that Della mentioned. Until it's out on the street there are issues about keeping things under wraps.

CHAIRMAN INSEL: Judith.

DR. COOPER: Right. I was just going to say what Story did. Then the problem would be with using our current working group is that maybe half, I don't know, but a large number of those people would really be in conflict in a sense because they might be likely to want to respond to some of the initiatives so they couldn't be part of it so we would have to start winnowing out folks who

are on the working group.

CHAIRMAN INSEL: Maybe it's worth actually clarifying what this is going to be about. It's actually very different than anything we have done up until now so you have to have people around the table who could answer the question if you look at some of these objectives, if you want a biomarker for early detection of autism before age 2, what would that cost?

Who will do it and how will it be funded? Which part am I willing to take on to fund and what money will I put into this in the year 2009/2010/2011? That is a different kind of conversation that we've had in any other of these groups. I think it's a different group of people.

You need to have people who know enough about the science to know what the feasibility would be, what the cost would be, what the best mechanism would be. Most of all, because this is all built on

partnerships, you would want to have people at the table who are going to say, look, I'll do this part if you do that part.

A good example of this recently came up around developing the brain bank which is one of the initiatives on here. Autism Speaks said, we=ll put in the following dollars to create a pipeline to get people involved. NICHD needs to be willing to support the repository if NIMH will actually pick up the distribution and the handling of the tissues.

That worked really well but that is the model this is all about. We need to have -- this is not just budgetary requirements. You have to have people there who know what these things actually cost.

Fortunately in that case we had people there who knew what a brain bank would cost if we were going to scale it up double, triple, quadruple. You also need to have the people who say, okay, this is what I'll spend.

I don't think you want a lot of people around the table who aren't willing to actually do the things that are on here and then be held accountable to them.

DR. LANDIS: So can I just -- reading some of the materials that we were given I have the sense that, once it's not completely transparent, there are issues of trust and priorities and whatever. One question might be, is there someone -- I'm making this up, I haven't discussed it with anyone -- someone from the workgroup who represents the public who could be a piece of that who would be able to say, yes, I sat in on those meetings. I don't know about the regulations piece. I sat in on those meetings and I have to tell you -- I can't tell you what happened but it's all okay. It's not a smoke filled room with mirrors where bad things are happening and the public monies are being siphoned off to do whatever.

CHAIRMAN INSEL: So, Della, if you

go to the slide of the groups that you were just starting as a kind of starting point, some of these are federal, some of these are private. There's a bit of a cross section and there is quite a bit of overlap with the workgroup itself.

MS. REDWOOD: I think we also need parents on this workgroup. I think the idea of having a person with autism, I think that needs to be included. I also think the other NIH agencies like NICHD and NIEHS that also fund autism research. So they are all going to be there as well?

DR. HANN: Right. Story is absolutely correct. NIH was viewed as the umbrella term for all of the relevant institutes.

CHAIRMAN INSEL: The NIH people know that if they don't show up their institute gets stuck with all this stuff that they don't really want to do. Everybody shows up for these things.

DR. LANDIS: It's interesting to think about while NIDDK, for example, digestive diabetes and kidney diseases has not been a piece of this workgroup, to the extent that there might be broader questions of co-morbidities in other systems, one would hope that their expertise and dollars might actually contribute if there were an initiative in that regard.

CHAIRMAN INSEL: Exactly. It's a great point. NCAM, NIAID, I mean, there are a whole series of NIH players we may need to bring into this conversation. We would add to this someone on the ASD spectrum as well as a family member or members.

MS. REDWOOD: We've had some great public members on the workgroup, Peter Bell, Mark Blaxhill that have been very involved. Denise Resnick. I would like to see if they could flow over to this as well. I'm sorry. There was another comment about these organizations.

I don't want this to appear as sort of a pay to play. You know, if you are going to fund research, then you can come sit at the table. It would be nice, I think. Autism Society of America is one of the oldest organizations and they are absent from this list as well as some national autism associations. Even though they may not bring dollars, they bring other resources to the table and I think they should have a seat as well.

DR. LANDIS: But if one of the issues here is to say -- I mean, the Muscular Dystrophy Coordinating Committee is another example of a committee like this. We came up with a plan and then each of the participating members was asked to identify a piece of the plan that they would actually take on as their particular goal and almost all those goals require money.

MS. REDWOOD: What about a goal of acquiring brain tissue? I know the Autism

Research Institute has just developed a trifold brochure that they hand out at all their conferences. They have paid for freezers to help store brain tissues. There's other ways to help provide the infrastructure without actually having money. You have resources of people.

CHAIRMAN INSEL: That's why ARI is up here. Are there other organizations? ASA as well?

MR. GROSSMAN: Well, yes. I'm just wondering how big is this going to be because I have a long list of people that I can add to this as well. It's just a matter of where we make these decisions. There is a whole host of organizations that represent state agencies or state agency directors, for example, or professional organizations that would be involved in the implementation of this.

CHAIRMAN INSEL: I think what you need -- I mean, at least from the way I look

at the tasks because there are only three. It's really a very focused group with a very small set of questions. It needs to be somebody who would know how to cost out a clinical trial, know how to cost out a study of biomarkers, that would know enough about the cost for developing cell lines for high throughput screening.

All the things that are in this plan people who can think about how to put numbers and then think about what part of that they would be willing to support in collaboration with others. That is the conversation that has to happen. If you think it's easy, remember that we asked the workgroup to give us budgetary requirements in their initial meeting.

As they said, we don't even know how to begin to think about this. There is a small group of people who do this for a living, program officers in these organizations who have this expertise. I

don't think this is something that very many of us would have the knowledge to be able to do with precision.

I want to reassure you that whatever comes out of this, like all these other committees this is advisory. They will send us information that we can then begin to chew on and decide whether to modify, accept, or reject.

Other thoughts about this?

MR. GROSSMAN: Again, how do you propose that we go about this? As I said, I have a long list of people that I can add to this. Do we just start throwing names out?

CHAIRMAN INSEL: Why don't we start with organizations that are here that would be able to have this kind of expertise and would be able to be real partners in this effort.

DR. LANDIS: Can we go back to what this group is going to do? There was a slide on that. Right?

DR. HANN: Is this the slide you're thinking of?

DR. LANDIS: So is this -- I hate to ask this. Is this group actually going to make the decisions about what will be done and to set priorities or is it going to figure out how much it costs, ask people to put forward their interest in helping to support these if it were done. I mean, I don't see this as what makes the decisions.

I mean, for example, a really high priority could be X and three groups agree to do X but in the end there is no applications which actually propose research that would accomplish X. I don't know, Tom, if I'm making these harder or easier for you -- for us.

CHAIRMAN INSEL: This is the most interesting part of the whole process because this is what everybody is going to care the most about. This is what is going to make this thing have legs. It's great to have good

ideas but someone has got to make it happen. I think at the end of the day that's money.

It's people saying, "This is important enough to us and to the community and we are going to invest in it." I would see this work, this implementation group, as the chance for people to come around the table and say, "We care about item 3.1 and we will invest to make this happen."

Like we just did with the brain bank piece and that was a nice and rather quick resolution of bringing a partnership together with the core competence of each of the three players and it was done. It wasn't all money. Some of it was in-kind contributions like Lyn was suggesting. That works. We have to do this through the whole plan.

The question I think you're raising is what happens when there is no one around the table who wants to do item 3.4 and, yet, the IACC has said, "We really want to see

this. We want to see a clinical trial in area X but nobody wants to do it." That is something we haven't dealt with yet and we'll have to figure out how that gets addressed.

I think as the initial step you want the people to say, "That clinical trial would cost $7.4 million and it would take three years and it requires 180 people to have enough power to be feasible and to be useful. We can't spend $7.4 million but we would be willing to contribute X dollars towards that end."

Something like that. That is what I would love to see come out of this. Maybe I'm fantasizing but I think until you get to that point this is just a document on paper.

MS. REDWOOD: Tom when is -- we still haven't established priorities yet so I'm just sort of concerned that we are putting this a little bit ahead of actually establishing our priorities for research. I really don't think we have done the best job

we could in terms of analyzing what has been done to date and what has really paid off and what our gaps are in the science. I almost think that we still priority setting before we move into this next implementation phase and we haven't really done that yet.

CHAIRMAN INSEL: We've tried. This has also been part of both these discussions. The workgroup was assigned to do that and you see what we've got. And the workshop struggled with it a little bit. I think where we ended up, and it's looking at this again in the minutes from the last meeting, was the decision that all 41 of the initiatives were of value.

They may be all above average in their interest level. Nobody wanted to lose any of them and there has been at that level sort of an unwillingness to set up a kind of rank order. What we ended up with instead was a set of short-term and long-term objectives with the idea that -- maybe I have

misunderstood this but tell me if I've got this right.

I thought the IACC was saying, "We want to do all of this. If it's a short-term objective in particular, we want to get going on it right away." There are not an infinite number of those. I think there are something like 13 or 14. Maybe there's a few more than that but it's a limited number across the six sections.

Now, when we last talked about this I thought the group said we do not want to set priorities across the six. We don't want to say that working on interventions is more important than working on screening so we do that first.

We want to try to take all of this on. I think your question is a good one because if we come to this implementation workgroup and nobody wants to do two-thirds of the objectives, then we are going to have to figure out how we want to wrestle with that.

Alison.

MS. SINGER: I think what I'm struggling with there a little bit is the concept that the NIH wouldn't pick up some of those areas. I mean, I think the private funders which are less encumbered by the CAA would have more leeway in terms of picking and choosing but that the NIH would need to be more rigorous in terms of following the recommendations from the strategic plan.

One thing I wanted to point out about this, I agree with this structure. I think it makes sense to have the funders at the table for another reason that wasn't brought up which is I think because we have such limited resources.

We've talked at many meetings about the actual dollar amount and there have been subsequent meetings where we tried to agree upon what the actual dollar amounts are that are being spent on autism and how we need to increase that number so that it rises to

the level that was appropriated by Congress specifically for autism research under the CAA.

I think we are still among the private funders and the NIH. A lot of the funding is duplicated so we really want to make sure and I think one charge to this committee would be to coordinate and understand who is funding whom so that a wide range of research can be funded and that not all the funding is going to the same places but that we are spreading the money more equitably and we are spreading the money in accordance with the plan. I think I would want to add to the charge of the committee, to the workgroup.

DR. LANDIS: In fact, having everybody sit around that table might help build the interest in doing that activity. It's not beyond belief that each of the organizations might want to have in their funding portfolio the stars even though that

might mean that the stars have perhaps more money than they can use effectively and so the kind of interactions that would occur at this group thinking about the plan and what people are willing to do might lead them to, "Well, gee, it turns out we are giving so and so X millions of dollars."

So are we and maybe we should think about is that the best use. I think it will be very interesting. I don't think this would be the final arrangement but just that initial meeting would be very interesting to see where the interest of the groups overlap or don't and what is left out and how we would deal with that as a community.

CHAIRMAN INSEL: Alison, isn't some of that happening already within this SWOG process getting the program officers together?

MS. SINGER: I mean, from everyone who is involved, I wasn't personally involved, it went incredibly well. It was very useful.

It is exactly the kind of thing that we should continue to do going forward and that is why I think it should be added to the charge to this workgroup to continue to do that. make sure that the funding is coordinated. Everyone understands what is being funded and why.

Again, I think the private foundations are going to have much more leeway and latitude to say we want to fund something that is not in the strategic plan and that is going to make it incumbent upon the representatives from the NIH institutes to pick up some of the Section C.4 as you described it.

CHAIRMAN INSEL: I guess it may be that there is more flexibility in the private foundations to fund work, for instance, that might not make it through peer review or might require a different kind of mechanism. Sometimes NIH is constrained by what it can do internationally. Some of these things talk

about a global approach.

The beauty of all of this is that everybody can play to their strengths and then bringing all that together we should be able to get something really spectacular done. I think you have to have the people at the table who are going to be able to work in this arena and who know how to do these very tasks.

DR. LANDIS: I also raise the issue of how we would assess whether or not strategies that we've taken in the past have been successful and should be continued. For example, NINDS has a program, I won't describe what it's on, which has become almost -- well, it's part of our portfolio.

It has been underway for 10 years. Everybody assumes it will continue to do it. This is not a disease related program. As we have begun to look at the successes of this program we recognize that it has not succeeded at what it was meant to do and that the money we're investing in it is not a wise investment

and we should rethink the issue and move those resources elsewhere.

I would hope that there is going to be that kind of assessment of ongoing programs and of new programs as they are set up. I don't know if we have strategies. It's like the peer review. There is going to be a mechanism now that will look at, okay, we make this change in peer review. Does it make it better, does it not make a difference, or does it make it worse.

If we have programs and they are not meeting the goals of the plan, then we shouldn't continue them. More flexibility again for the private foundations who can at the end of a year say, "You didn't meet your benchmarks. We're going to close it."

MS. REDWOOD: Story, I was under the impression that in July of '07 the institute created an Office of Portfolio Analysis here at NIH and so could we not ask for their help and actually looking at our

autism portfolio and analyzing our successes using bibliometric data?

I also wanted to say that in the past the IACC developed a roadmap and it was investigator driven. When you actually looked at what NIH funded and you looked at the roadmap there were all these gaps. These funded initiatives were trying to be retrofit back into the roadmap.

I really think we need to look at some type of re-engineering of our funding process where we do identify priorities and we actually go out with RFAs and create special emphasis review panels to get these very high priority research projects done and create ways for that to happen.

I also want to put in a huge plug for the bottle that was developed by the Institute of Medicine that is utilized by the Department of Defense and their research efforts and that it brings to the table stakeholders, scientists and researchers to

review projects. I would really like for that to be a consideration as well in terms of what other types of tools and methods we can use to make sure these high priority research areas get funded.

CHAIRMAN INSEL: That is part of why the funding tools issue is up here and this idea because we have heard this before, the methods of peer review and the concern that while peer review is brilliant at identifying scientific merit, there are areas that may not -- that we may need to address that may have difficulty in peer review so the question that came up about using this workgroup to also recommend some alternative approaches and to be thinking -- a lot of this will be RFA driven with special emphasis panels.

I think that was the assumption going forward is that will be the way. If you are going to make new investments, that is the way this is likely to happen. I would assume

those items will be part of their charge. What I'm hearing you now say is that you want them to do a full portfolio analysis and kind of redo the SWOG with measures of outcomes of each of their investments.

MS. SINGER: I don't think it has to immediately be redone but I would say periodically this group would want to do a SWOG analysis. I mean, I think the work that was just done is sufficient for now. They should review it.

MS. REDWOOD: Tom, one of the things I mentioned at the last meeting and it did seem to have some support but we never took a vote was actually starting a committee like we have our services committee that would be our strategic planning committee so that each year there is an ongoing group that could report back and work on these things like the SWAT analysis.

I know not everybody here has as much interest in this as other members do but

I would like to put that suggestion back on the table as well to sort of be a segue between out committee and these different implementation workgroups and people that we bring in.

CHAIRMAN INSEL: We did talk about that at the last meeting and I think there was a sense, again looking at the minutes, that at least many people thought this needed to be the work, at least at this point, of the whole committee. My hope is we won't have to go through this every year.

When we get to the November meeting and we can agree on what the strategic plan 1.0 looks like that there will be a subgroup that will help us craft strategic plan 1.1 for the next year because every year it's going to be a different -- it's going to be updated.

I'm not sure that the whole group wants to go through this process every three months for the next four years. That may be

the point if we can table this suggestion. If you can bring it back in November, I think then we want to look at the possibility of forming a subcommittee like we are doing for services that will really take us on.

Lee.

MR. GROSSMAN: I hate to come across so dour but I'm very uncomfortable with the implementation workgroup as it is being proposed. We heard about this at the last meeting and just didn't like it but I figured I would see how it develops and listen to the discussion and I still feel very uncomfortable about it.

To call a selected group of people into a room and these are the terms that have been thrown around here to kind of divvy up what the public body has formulated in terms of strategic planning to decide who may or may not fund or be involved with what I think is potentially hazardous in the entire strategic plan.

I could see many biotech firms, pharmaceuticals, beltway bandits as some of them are called, and other member organizations. The list goes on and on of people that would want to be involved in this and could see themselves as, "Hey, I could do that." I just think we are treading some very dangerous ground here.

In many ways it does sound like a smoke-filled backroom where you are making decisions that will affect the entire autism research portfolio going forward. I would hope that we would find a way to engage many, many others out there that we haven't tapped yet that have incredible resources and certainly have an interest in investing in autism. This will essentially shut the door on any of their future involvement.

CHAIRMAN INSEL: So maybe we should clarify a little bit because I don't think that anybody wants this to be the full story nor to -- nobody wants this to be

shutting anybody's door. The problem I think the committee has is that the act requires that for every part of the strategic plan we put in budgetary requirements.

Let me just read you a few of the objectives. Launch three studies that specifically focus on the neurodevelopment of females with ASD by 2011. Complete a large scale multi-disciplinary collaborative project that longitudinally and comprehensively examines the biological, clinical, and developmental profiles of children with ASD as well as typically developing children from early development through school age by 2020.

Now, we need to put dollars on that. I haven't heard anybody step forward and say, "I can do that. I know how to do this. I can tell you what these three trials on the neurodevelopment of females with ASD will cost and I can tell you how to get it done by 2011." Tell me who can do that for us. That is what we want to have on this

workgroup.

We have tried this before and we failed miserably and we have asked other people. This was exactly the charge, set priorities and give us budgetary requirements. We did this back in the winter for the workgroup, the first strategic planning workgroup and we got zip to be very blunt about it.

We got no budgetary requirements back and absolute refusal to set priorities so it's back in our laps. I don't think anybody here at the table has this expertise. Tell me who else can do it for us if we are not going to use the people that are sitting in programs that do this for a living.

DR. LANDIS: It's going to come back here so it's not that it would disappear into the ether. It would be a report that would come back here and people could say, "Gee, no that price tag is too high and couldn't we figure out some way to make it

less?" Given that this cost a billion dollars, maybe this isn't as important as these other five things that you could get done for the same amount of money.

CHAIRMAN INSEL: We need to know are there people out there. I mean, you can mention biotech companies or people from PhRMA who could help us with this. It is a different -- PhRMA does trials in different ways. It usually does them offshore. They tend to out-source to Eastern Europe or Asia. They have a different way of pricing things. Maybe not a bad idea to have someone with that perspective at the table so that they could give us a different set of numbers. I think we just -- what we are talking about here is real nitty gritty expertise in financing science and getting experiments done.

I must say I don't think the people around -- just speaking for myself I don't know how to put numbers on this. I

think most of us don't have that experience. There are people who do it for a living and those are the people who are trying to get onto this implementation group.

Lyn.

MS. REDWOOD: Tom, I just have to disagree with what you said about the strategic planning workgroup in that they refused to do it. They refused to do it under the constraints that they were given. With regard to the priority setting they couldn't prioritize across categories.

They disagreed with the arbitrary nature of how they had to assign points. I'm sure they would love to do a budget but they couldn't do it in one day and they didn't feel as though they had the resources yet to be able to do that. I think we are premature in really dismissing them.

Peter, you are key on that workgroup. I didn't get that as the take-home message that they just refused to do it or

said that they didn't know how to do it. They didn't have the time to do it and they didn't have the tools and the resources they needed to do a good job.

CHAIRMAN INSEL: Well, we didn't get it. We gave them two charges. This was one of them and for whatever reason we didn't get it. I would submit that the kinds of skills that I am asking that we have in place are not the -- that's not what people were selected for on the workgroup, on the group that we have now.

That really had a different mission. It was probably our mistake to think that was a group that could fulfill this particular requirement. I think it was a mismatch. What I'm suggesting is we need a different group of people who do this for a living to help us get this done quickly.

There is no magic here. There are people who develop RFAs. That is what they do for a living and they have to make a decision

what a clinical trial is going to cost. Those are the people we need to provide budgetary requirements.

If you can figure out some other way to do it, that would be great but so far I've got to tell you we are six months out in this discussion and I haven't seen a budget requirement for any of these except for the one on developing the brain bank.

My hope is that we could put people in a room, lock them up, give them this assignment, and give them a time frame in which to get this done and they will have to walk through this.

The question of the accountability and who is going to do what is a different set of issues but we've got to get the budgetary requirements done so that we can meet the requirement of the Combating Autism Act. I don't think we're going to do it as a committee so tell me who else should be on this implementation group.

DR. TREVATHAN: In a previous life I designed some clinical trials and put price tags on them. What concerns me, and I agree with everything you said, once you start getting into clinical trials of things like this, all of a sudden the confidence intervals around these estimates become pretty significant.

Like the clinical trial that you just mentioned a little while ago as an example is at $7 million. What happens if that is really $20 million and our estimate that we have that we put in actually is 7? I mean, the people -- I agree that we need to have at this phase the people that really know how to do the budgetary calculations and estimates for these trials that have a track record of being accurate.

That is usually not the scientist. It's usually not the people that run institutes or centers or advocates. I agree with you it's a different group and it's

important. We want them to be as accurate as possible or we are going to find ourselves in a budgetary problem down the road trying to implement these things.

CHAIRMAN INSEL: Any other ideas here?

DR. JANVIER: I just think we need to kind of move on and take a vote on this.

CHAIRMAN INSEL: We are just about to. Can I have a motion?

DR. JANVIER: It's not my field but it seems -- I make a motion to approve the list, wherever that is, with the addition of a person with autism, a family member of a person with autism. The Department of Education we wanted to add also.

DR. HOULE: I would be glad to be a member. As it's defined we don't cost out clinical trials per se it looks like in the requirements that you want. I would be glad to sit in and see what I can contribute to the group in terms of this kind of science.

Please feel free to include me and I may be able to help somewhat with the process.

CHAIRMAN INSEL: Okay.

DR. JANVIER: And the priority for the group should be the budgetary requirement secondary I would think would be -- I'm sure Alison has people that work for her that know what it cost to do certain things and that is really a secondary issue as to we are planning on going in this direction, this direction, this direction anyway and we are putting this much money towards it but the priority has to be get the budget estimate done and then move on to the secondary issues that were on some other slide there.

CHAIRMAN INSEL: That's a motion. Is there a second?

(Seconded.)

CHAIRMAN INSEL: All in favor? Opposed? So we've got two opposed but the motion carries. Okay. We will take a break.

Christine.

MS. McKEE: The very first slide that you showed talked about public comment on the draft strategic plan. We never got back to it. It talked about -- there you go, focus groups. I know we like RFIs but one of the things that I struggle with on this committee is that communication is always in one direction.

We never get to talk to the public. They sit out there. Every once in a while someone comes up and gives a speech. I don't know if it's appropriate with the strategic plan or with the services subcommittee. I think at some point it would be great to have a two-way conversation with the public.

I think a focus group is a wonderful way to do that where we can sit down and really talk through what we're doing and hear from them about their life experiences. I would also propose that we do it -- I've had this conversation with Joyce -- in the midwest

for a rural community or an under-served community.

I would like to get out there a little bit more than sitting on the coast and looking at these issues and populations that are highly served. It's not perfect service, I complain a lot, but I would instead of just sticking with an RFI for everything like to get down and have two-way communication with the public.

CHAIRMAN INSEL: Alison.

MS. SINGER: I think that makes a lot of sense. I think what you are describing, though, might have a better application in a webinar because as we have seen from all of the meetings we've had, we have so many people who are eager to participate and share their views and in a focus group you are by definition limiting it to 12 people who someone randomly decides are representative.

You don't get as broad -- you

don't offer as many people an opportunity to share their views. I think that is a great idea and I would say maybe we open it up and not have the public only be on silent but actually hear from more people and have a dialogue.

CHAIRMAN INSEL: Other input on this?

MS. BLACKWELL: So are you talking about like, Alison, sort of a remote town hall meeting where people call in?

MS. SINGER: Virtual town hall meeting.

MS. BLACKWELL: Okay. That's kind of what I was thinking, too.

MS. REDWOOD: Tom, I think it would also be nice, I know during our different workgroup meetings we've had the opportunity to dial in and listen. I think if we would allow the public also the opportunity to dial in and listen to our wonderful discussions here at the IACC, that would

really help to increase transparency with what is going on and for people to be able to keep pace of this whole strategic training process.

I also would really like -- I understand there are transcribed minutes to the meetings. The summary minutes are great but it really doesn't capture a lot of the rich discussion that transpires during the meetings. It just sort of captures some of the decisions made so I also would like to ask that we somehow have those transcribed minutes be up on the internet as well with the other documents.

CHAIRMAN INSEL: Della, are there limitations to having the meetings themselves available for people from outside to at least listen in?

DR. HANN: Well, there are cost issues and that also will dictate where we can actually convene the meetings because you have to have a room that is equipped to be able to have that kind of feature added to it.

I think the other piece of it, which I do need to speak with our legal counsel about, has to do with federal record keeping. There are requirements when you have a federal meeting, particularly under FACA, so the meeting summaries that are prepared are kept in perpetuity.

They become a standing document that has to live on and the government is responsible for maintaining over time.
I don't know and I have to get legal counsel advice on what happens when you have more than one of those records. I need legal input in terms of that to be able to answer and provide more information.

CHAIRMAN INSEL: Okay. Back to the question about the options here. We've had some interest in focus groups, an interest in webinars. No one has yet spoken to town hall meetings but that is also a possibility. Other ideas about the way to get public comment?

DR. LANDIS: I think it's not just public comment but also communication about the plan and the activities and what's going on.

CHAIRMAN INSEL: Cindy, do you want to say something about town hall experience?

DR. LAWLER: Well, I think it speaks to what Story just mentioned. I envision maybe a series of town hall meetings or sort of a plan that this committee comes up with for ongoing dialogue and sort of education and two-way communication thinking about or restricting it as, "Okay, let's have another town hall meeting so we'll get public input on the draft version," is probably not in the best interest but if we could think about it sort of long-term it may even be something -- do a virtual town hall meeting as part of the rollout of the strategic plan.

Just going forward in time and using a variety of mechanisms to engage the

public, town hall meetings being one of them. I agree that the RFI is one way communication. It's very static. You get the sense that they are just collected and they go in a black box somewhere so I would support sort of a diverse mechanisms including town hall meetings. As you know, the one that we held in May was, I think, pretty successful.

DR. HANN: Can I just ask a point of clarification? Cindy, I heard in what you just said to think of this in a phased type of way.Maybe I'm over-interpreting what you said.

DR. LAWLER: My comment is to not just sort of do it on an ad hoc basis, "Okay, here is another place we need public input. We can do A, B, or C."

DR. HANN: Right.

DR. LAWLER: But to think more long-term that we should be doing -- you know, having a series of dialogues be it town hall meetings or RFIs, especially given that we are going to be updating this plan every year.

DR. HANN: Absolutely. Absolutely. I guess I will admit I have sort of semi-blinders on in terms of between now and November in trying to figure out how to accomplish everything. Again, this may be wishful thinking on my part. What I heard you say was a possibility of thinking about for right now in terms of getting comment on a draft the RFI seems like a viable means by which to do that.

It's not clear from what you just said if the town hall/webinar has something to do with this immediate juncture or if that might be more aptly done once the plan has been concretized and then we start on the next phase in terms of gathering additional input, etc., and feedback from people about what they think about the plan.

MS. BLACKWELL: One of the possibilities that Cindy and I talked about just in terms of future meetings with the public is that HHS has 10 regional offices

across the United States. Every one of those offices a large meeting room that holds 100 or 200 people which would have been sufficient for the group that you guys had in Sacramento.

And also capability to hook up visually to each other. I have often thought that may be one way for us to at least -- we could even hit 10 major cities at once, San Francisco, New York, Denver. The list goes on. We do have that capability within HHS.

CHAIRMAN INSEL: I'm hearing two things. One is the need to have a real plan for the plan or a plan for dissemination and a plan for connecting, communicating, getting input, getting clarity and transparency.

The other piece I'm hearing is we need some direction about what to do between now and November 21. The RFI will happen. Does the group want to see us bring in focus groups, webinars, or town hall meetings between now and November 21st? Not urgent? Maybe something to do with the next phase.

Everybody want to go to lunch? Okay.

Della, I'm reading their lack of response as maybe this needs to come back with a more thought-through plan that takes all of these options and really has not just a two to three-month window but a two to three-year focus on what do we do next and how do we get this out there so that the next phase of the plan, that is 2009's version, will have maybe all of these things happening and in a very organizational way so people will know well ahead of time.

I suspect that what we need to do between now and November is get something together that can be submitted. Maybe we meed to really focus on that if that's going to work for everybody.

Okay. Thank you very much for taking us through this. Let's stop here and we'll a break until 1:15. There is a cafeteria directly above us and we'll reconvene at 1:15 to hear from Dr. Mark Bear

and Dr. Koroshetz.

(Whereupon, the above-entitled matter went off the record at 12:26 p.m. and resumed at 1:15 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:17 p.m.

CHAIRMAN INSEL: It's a pleasure to introduce Mark Bear. Mark is an investigator at MIT. He's also the Director of the Picower Institute for Learning and Memory and a professor of neuroscience at MIT.

Mark is well known to some of the people here because of his long-term interest in synaptic plasticity and in development and his more recent interest in Fragile X as an example of a place where we are making tremendous progress in being able to link an understanding of a disorder at the molecular and cellular level to actually now developing new therapeutics.

We thought it would be useful for

the IACC to hear this particular story. It's not entirely about autism but it's about a related disorder in which 30 percent of the children meet criteria for autism. Because of this kind of progress it points the way for the kinds of research that we think might also be very useful for the rest of the children with autism who don't have Fragile X.

Without taking anymore of your time, Mark, thanks so much for coming. We are looking forward to your presentation. I hope you will be able to take some questions at the end as well.

DR. BEAR: Thank you, Tom. I hope everybody can hear me okay. It's a pleasure to be here. Let me just begin with a slide that makes a point that is obvious, I think, to everyone here which is that proper brain function requires precise connectivity between neurons.

I think this is nicely illustrated. Unfortunately these slides

aren't projecting very well today but it's nicely illustrated by just taking a look at the organization of the ascending visual pathway where we have projections into the brain from the eyes, right and left eyes, and they project up into the cerebral cortex.

It makes the point that even though we have two eyes, we have a single percept of visual space and that single percept of visual space requires very precise mapping of these homotypic points in the backs of the eyes in the retinas on individual cortical neurons so binocular vision requires precise connections as does every other brain function require precise connections in the brain.

So where do these connections come from? How do they arise? We can sort of look at this development and modification of synaptic connections in the brain as occurring in four different epochs across the lifespan. Prior to birth and at about the time of birth

there is a huge synaptogenesis in the brain. Neurons are emitting axons that find their appropriate targets.

Once they find their targets they start to form synaptic connections that are the basis of electrical and chemical communication between neurons. This large period of synaptogenesis occurs prior to birth. It's experienced independent, largely activity independent and it's a process that is guided by genetic instructions.

However, after birth between the time of birth and adolescence there is in addition to ongoing synaptogenesis creation of synaptic connections, there is a very active process of loss of synaptic connections. There is an ongoing process of whittling away inappropriate connections or connections that are not currently used for information.

It's during this period of development that there is a very important role for experience so that the brain really

develops precise connectivity under the influence of experience.

This process of bi-directional synaptic change, synaptic gain and synaptic loss persist throughout adulthood and is likely to be the basis of adult learning and memory. We know that in the senescence period the process of synaptic loss reemerges with a vengeance and is likely responsible for cognitive decline.

Now, disruptions of this process of synaptic development and plasticity give rise to a number of diseases that we might call synapsopathies. Examples are synapsopathies that occur during development and that would include autism, mental retardation, schizophrenia as examples. There are synapsopathies that emerge during senescence hastened by diseases such as Alzheimer's disease that lead to cognitive and degenerative disorders.

So it's the belief of basic

neuroscientists that to gain understanding of these disorders of synaptic function and plasticity we need to study it at a basic level.

Many of us for many years have studied the basic properties of synaptic plasticity and a very classic model was actually provided 40 years ago or so by Hubel and Wiesel at Harvard that showed that simple manipulations and visual experience such as patching one eye would lead to changes in synaptic connectivity in the visual cortex that can lead to blindness.

This is a very powerful model which we study the role of experience in synaptic development. Patching an eye would lead to the weakening of some connections. It causes blindness and the strengthening of other connections. It compensates for the loss of that other input.

We've been working hard on trying to understand the basic mechanisms of this

process. We understand now that a lot of the action occurs at synapsis that use glutamate as a neurotransmitter. This isn't surprising because glutamate is the major neurotransmitter of the brain.

It's the neurotransmitter of 80 percent of the synapsis in the brain. It's the neurotransmitter that mediates most synaptic exitation in the brain.

We know that these glutamate synapses, or glutamatergic synapses, can be modified by patterns of electrical activity caused by different qualities of sensory experience.

These modifications are triggered by activation of glutamate receptors and they often are manifest by changes in distribution of glutamate receptors so it's a very active area of inquiry studying how glutamatergic synaptic transmission is modified by experience both during development and the establishment of proper connections and also

in adulthood as a basis for learning and memory.

Another thing that we've learned is that the appropriate modification of glutamatergic synapses requires the timely synthesis of new proteins. When I say synapses are modified, I mean they are either constructed or they are taken apart and part of those processes require the synthesis of new proteins at the synapsis, proteins that might glue synapses together or be used to break synapses apart.

There is a very active regulation, a precise regulation, that couples neural activity in the brain to the synthesis of new protein. This occurs both at the transcriptional step. This is something that occurs in the nucleus where genes are transcribed into messenger RNA and also at the translation step where the blueprints provided by messenger RNA are translated or used to instruct the synthesis of new protein.

We know that translation can occur specifically at sites of synaptic transmission and can be regulated by activity at individual synapsis. So a view that's emerged over the last several decades is that optimal neural network performance requires an optimal level of synaptic protein synthesis.

I have just sketched out here a function of what it might look like where we have neural network performance on the Y axis and synaptic protein synthesis on the X axis. We know for a fact that if you take a normal individual, an animal model or a human and you interfere with protein synthesis, you slide that red ball to the left and you see an impairment of neural network performance and you'll see a cognitive impairment.

There has been actually a lot of interest in the field of cognitive enhancement to try to promote synaptic protein synthesis as a way to restore proper synaptic plasticity to those who lack it. However, like many

processes in the brain the dose response function is what we call an inverted U shape so there is such a thing as too much of a good thing.

There are some disorders where this ball is slid to the right and we actually see an impairment of synaptic plasticity or the proper adaptation of synapsis to the environment because of excessive protein synthesis.

It's very important that there are precise mechanisms and machinery that will enable the supply of synaptic proteins to keep up with demand. Since it's such a critical part of synaptic function it's going to be a tightly regulated process.

What we have learned really just in the last five or six years I think is that a very major mechanism by which protein synthesis keeps up with demand is mediated by a glutamate receptor called metabotropic glutamate receptor 5.

You remember, again, glutamate is the major neurotransmitter in the brain so the more active the brain is, the more glutamate is released and there is a greater demand for protein synthesis and a way that demand is registered is by activating this metabotropic glutamate receptor 5. There is very good evidence that this receptor drives protein synthesis at individual synapses in a very precise way.

Our brains are loaded with mGluR5. This is a recent PET study showing the distribution of mGluR5 in the human brain. You can see that in all the regions of interest, regions of interest to me, like the cerebral cortex. Even in the cold regions there is actually another receptor called mGluR1 that serves a similar function. For example, in the cerebellum.

So it's a machine and it is very complicated. Of course, my diagrams are gross over-simplifications even including this one

which has a lot of arrows and letters and numbers. A key starting point is the metabotropic glutamate receptor and there are other receptors that are actually sensitive to activity that can drive or regulate protein synthesis.

Activating this receptor will stimulate activity of a complicated biochemical pathway that ends with the translation of messenger RNA at synapses into protein. Some of the elements of this pathway that are indicated with asterisks are negative regulators of protein synthesis.

Like any good machine there things that push it forward and there are other things that hold it in check so a number of negative regulators. The one that I'm highlighting here with the arrow is a protein called FMRP.

A way to simplify this diagram is to just consider the fact that we know that we can drive protein synthesis with the

metabotropic glutamate receptor and we can break it with the protein called FMRP. You can imagine this is just like the accelerator and brake on a car. Proper function of the car requires proper function of both of these elements to control the car.

The reason I'm highlighting FMRP is that this is the protein that is missing in the disorder called Fragile X syndrome. Fragile X syndrome is a single gene disorder that is caused by the silencing of a gene called Fmr1 and as a consequence there is a loss of this protein, FMRP.

As a consequence of the loss of FMRP we now know there is excessive protein synthesis in the brain. This is quite a dramatic difference actually. I think it was most clearly demonstrated by some work done at NIMH by Carolyn Smith and we have also been able to repeat all these studies using different methods. There is a general consensus in the field that a problem in the

Fragile X brain is a 20 percent increase in the rate of ongoing protein synthesis at synapsis.

So Fragile X has a number of features. It's a syndromic disorder. It has a number of features in common with autism or an autism spectrum that are listed here. It's the most common inherited form of mental retardation. About 20 to 30 percent of the children with Fragile X will satisfy the full diagnostic criteria for autism.

As a cause of autism it actually is a minor cause. It may account for about 5 percent of the cases in autism. Yet, it may provide critical insight into the pathophysiology of autism spectrum disorders. By pathophysiology how is brain function altered by genetic mutation that leads to an autism spectrum disorder.

So, in a sense, Fragile X may be at the van guard really of fulfilling the promise of molecular medicine. That is to say

that there has been a huge effort to understand the genetic bases in human psychiatric and neurological diseases.

An excellent example is Fragile X. It was a product of the human genome project. It's a single gene disorder. We have identified the gene and because it's a single gene disorder you can model it in animals.

A number of different organisms can be used to model these single gene disorders including fruit flies and zebra fish and mice -- famously mice. It's possible to create a mouse that has the same genetic defect as a human Fragile X. Namely, a silencing of this Fmr1 gene and a failure to produce that protein FMRP.

With that mouse model then we can go in and say how is brain function altered. The cause of Fragile X is the silencing of the Fmr1 gene but what we really want to know is how does this interfere with normal brain function.

So we and many other labs around the world have gone after this question and I don't have time and you probably don't have the attention span to listen to the whole thing but I can tell you that some of the consequences are pretty dramatic.

For example, with too much protein synthesis in the Fragile X brain there are too many synapses. This can be revealed using a particular type of stain that will stain dendrites, neuron dendrites. These dendrites emit these little structures called dendritic spines at the site of glutamatergic synaptic transmission.

In a normal mouse this dendrite would have spines with the density that is shown here in this example. But in the Fragile X knockout there is a proliferation of spines. It's about a 20 percent increase in the density of dendritic spines so hyperconnectivity, over connectivity.

What we think is happening in

Fragile X is there are too many synapses and the synapses that are there are too weak. It's really an imbalance in synaptic connectivity.

What we can do is we can quantify this difference by applauding the density of spines against the location on the dendrite and so typically where you study -- where in the dendrite you study it there will be differences in spine density but this is the wild type profile I'm illustrating here and I hope you guys can see it over here. That is the wild type profile.

In the Fragile X you can see this curve has shifted upward by about 20 percent. There is a significant increase in the density of dendritic spines. That is one consequence of exaggerated protein synthesis and synapses.

So, again, Fragile X, we are missing this negative regulator. It's like driving a car with no brakes. You just tap

the accelerator and Lord knows what could happen. One thing that could happen would be too many synapses. We know that the accelerator in this system, or an important accelerator in this system, is the metabotropic glutamate receptor.

This is the receptor that actually is the driver of protein synthesis. The question then becomes could we correct aspects of Fragile X syndrome by taking our foot off the gas so try to restore normal balance of protein synthesis.

There are a number of ways one can do this and the most therapeutically relevant way is with drugs and I'll tell you a little bit about that in a second. The most definitive way is to do it genetically. Again, because of the power of mouse genetics, we could create a mouse that has a 50 percent reduction in the mGluR5 receptor.

So we just knock out one copy of the gene and we can produce a mouse with 50

percent of the mGluR5 receptor. Then we can ask what happens in a Fragile X knockout mouse if it's crossed with an mGluR5 deficient mouse. Could we now restore normal protein synthesis and normal brain function.

It's called a genetic rescue strategy. The logic is here is the normal balance between mGluR activation and breaking by FMRP. In Fragile X we are missing the brakes so we get exaggerated consequences of activating this receptor.

Now I can create a mouse that has 50 percent of the normal level of receptor. We can ask, will this restore normal balance when this mGluR5 heterozygote, which you call HT, is crossed with the Fragile X knockout which we call KO and the resulting animal that we call the cross or CR.

So what happens? The first thing that is encouraging is that the reduction in mGluR5 by 50 percent alone has no effect. This is again looking at the density of

synaptic connections on these dendrites in the mGluR5 heterozygote that has half the normal level of mGluR5 receptors. There is no difference at all compared to the wild type, the normal animal.

But when we cross the mGluR5 heterozygote with the Fragile X knockout what happens is we get a complete rescue. I mean, a really remarkable result so that we can completely restore the normal density of synapses in the cortex in this case.

Now, that alone I think would be a fantastic finding, but that is not the only thing that has been measured. Fragile X knockout mice have a number of mutant phenotypes, that is, differences between the Fragile X animal and the wild type. We studied many of these in my lab and this is a complete list.

I don't need to go through what each of these things mean, but I can tell you that of all these things that we studied, all

these aspects of function that we've studied we found them to be exaggerated in Fragile X. An example would be rate of protein synthesis which is increased in the Fragile X knockout mouse.

I showed you the increase in spine density that is exaggerated in the knockout mouse. In the mGluR5 heterozygote, that is the animals with just 50 percent of the normal level of mGluR5 you can see this alone has very little effect, with the exception of one of the things that we measured.

When we cross the mGluR5 heterozygotes with the Fragile X mice we get a complete rescue of, it looks like, seven out of eight of the phenotypes. The reason this is extraordinary is that each of these assays taps into a different circuit in the brain.

This is a general probably brain-wide problem of excessive protein synthesis and various consequences of that depending on the circuit. All of these can be corrected by

decreasing the expression of this mGluR5 receptor.

So what we think then is that in Fragile X we think that the problem is that as a consequence of this single gene mutation is that there is excessive protein synthesis, so we push that red ball to the right shoulder and see impaired function which includes cognitive function, social behavior, communication, and even functions outside of the central nervous system such as irritable bowel.

The pathway that I've outlined for you is one that where glutamate drives mGluR5 which drives protein synthesis and there are varied consequences including proliferation of dendritic spines.

Now, these steps can be targeted so a goal then is to ask can we do manipulations that will slide the red ball back to the optimal level. Can we reduce this synaptic protein synthesis and there are a

number of ways to do that. You can modulate the release of glutamate. You can antagonize the activation of mGluR5. You can use direct inhibitors of protein synthesis.

The full promise of human genome project and molecular mechanism is to go from pathophysiology back to novel therapeutics based on this information. We are right now about ready we hope to close the circle. We have discovered some of the disease pathophysiology, excessive protein synthesis and the multiple consequences of that.

We have identified a therapeutic target which is the metablature of the mGluR5. There is a big effort underway to develop compounds that will selectively interfere with signaling so we can recreate with a drug what we were able to do genetically in the mouse.

That is to say, for example, reduce signaling through mGluR5 by 50 percent. The hope is that by doing that we may be able to restore normal function in humans as well

as mice. There has been a lot of progress made in this. There are compounds available that block mGluR5 that are not approved for use in humans but can be used in animal models.

There has been now quite a large number of studies using these drugs in various Fragile X models. This is now an obsolete list. It's probably twice as long now as when they made it.

A drug called MPEP which is an mGluR5 antagonist has been used by a number of investigators, again around the world looking at different aspects of Fragile X in the animal models ranging from the mouse to flies. Not shown on here is the zebra fish model. Amazingly treatment of these animals with this drug has been shown to correct multiple aspects of Fragile X syndrome in these widely different model organisms.

So there is certainly proof of principle. We validated -- we and researchers

around the world have validated mGluR5 as a therapeutic target in Fragile X. This year there are three pharmaceutical companies that have initiated human clinical trials of drugs targeting mGluR5 for the treatment of Fragile X syndrome.

So I have highlighted that we have a complicated molecular machine that couples, in this case, synaptic activity or glutamate mediated activity of synapsis to protein synthesis. For this machine to function properly requires a number of checks and balances so we have a driver of activity.

We have a number of checkpoints. The one I illustrated here is FMRP. I have circled some of these other ones and interestingly single gene mutations in these different elements also cause disorders that are on the autism spectrum.

I think one that actually received some very recent attention is the mutation of the tuberous sclerosis gene that leads to

tuberous sclerosis and what my colleague at UCLA, Alcino Silva, found was that he could correct multiple defects in the tuberous sclerosis knockout mouse by giving them a drug that knocked down protein synthesis.

The Tsc1 and Tsc2 proteins are negative regulators of protein synthesis mediated by a protein called mTOR. There is a drug that will selectively inhibit mTOR.

What he found was that by pharmacologically inhibiting mTOR he could overcome the disinhibition by the loss of these proteins and restore normal function. These are very exciting results that we can possibly correct genetic defects with pharmacological treatments once we know the pathophysiology.

I am sure you have all heard about the recent study published by my Boston colleague Chris Walsh and Mike Greenberg at Harvard where they identified genes, deletions, and a number of variations that

lead to autism. The surprising finding was that the genes that they implicated were genes that were regulated by activity. Probably also genes involved in the coupling of brain activity to protein synthesis.

So it has become very clear that many of the genes implicated in autism appear to fall within a pathway that couples brain activity with synaptic protein synthesis.

Some of the single gene mutations like neurofibromatosis and tuberous sclerosis and Fragile X may be involved in the regulation of translation, specifically at synapses and other causes, other mutations maybe interfering with the regulation of transcription at the cell body. In any case, it is a suspicious coincidence that so many of these genes seem to fall into this core mechanism that couples neuroactivity with protein synthesis.

Knowledge of this pathway has suggested novel therapeutics for autism

spectrum disorders that are now in clinical trials. I think we can look forward to more and more development of therapeutics that are targeting this pathway.

I just want to conclude by thanking all the sources of funding for my work. Thanks to Tom and the NIMH for Conte Center grant that we've enjoyed, NICHD for R01, NINDS for a center grant.

The Eye Institute which is not represented here but it was really our basic studies of the visual cortex that led to a lot of the insights that led to this, and the private foundations, Howard Hughes Medical Institute, FRAXA, and the National Fragile X Foundation, the Simons Foundation, and the Boston Autism Consortium. Thank you.

CHAIRMAN INSEL: Let's take about five minutes for questions. Five or 10 minutes. Questions?

Alison.

MS. SINGER: Thank you so much.

That was incredible. I wanted to ask about when you talk about restoration of function in the mouse, how old is the mouse at the point where you are able to restore function? Do you think that will translate when we start to try to revert to restore function in humans?

DR. BEAR: Yes. That's a great question. The -- so -- of course, the answer is a little bit detailed but in our own studies, of course, we are knocking down mGluR5 from conception because it's a genetic manipulation.

However, normally mGluR5 expression doesn't come up until after birth in a mouse anyway. So we think that the consequences are post-natal. It is a post-natal reduction mGluR5 expression. But it is a good -- you know the obvious question is if you introduce therapeutics late in development how much chance to you have to correct damage that may have already occurred.

And I think that that is where we

are actually very encouraged by a lot of the drug studies. So, this drug MPEP has been shown to have beneficial effects even when it's given to adults -- adult animal models including flies and mice. So we think that we should have the opportunity to have beneficial effects by coming in late. But obviously the earlier we could start it the better.

CHAIRMAN INSEL: Can I just add to that. There are two other stories that have developed in parallel. One Mark mentioned which is the tuberous sclerosis story and the other is the neurofibromatosis story. And in both cases there was mouse studies, just like you heard.

But there we actually already had clinical studies completed. And on the Ts one, while not yet published, it looks very much like the human data which is in older children, I believe, and young adults. It is quite effective at rescue using Rapamicyn, the

drug that you saw in the mouse project that Alcino Silva did.

The NF1 story is published. That just came out maybe two months ago in -- month ago in Nature Medicine. In that case, in fact, that compound, which is a statin, which works beautifully in the mouse, also works really beautifully in humans. And I believe that that case it was young adults as well, though you may know that better than I do.

So with that precedent there is good reason to think that these syndromes like this, which we used to call globally mental retardation with the idea that all you could ever think about was rehab we are now beginning to rethink that whole concept and considering that maybe even in adults you could go in and rescue cognitive function, that mental retardation is not a life sentence in that sense. It just hasn't been treated yet. Very different concept of this whole

area.

DR. BEAR: And really a sea change just in the last couple of years. And the other thing about when therapeutics are introduced then we may -- without even knowing the underlying cause of many cases of autism. If they respond to a drug treatment that we know will dampen down synaptic protein synthesis, it suggests that those different causes share the same pathophysiology.

And I think that is the importance of the single gene disorders and the ability to model them in mouse. So, I mean, already we see with a number of different single gene disorders that we=ve modeled in mice we start to see them falling into this pathway. So this is the real hope that we have.

DR. LANDIS: So, one of the things I find interesting is Fragile X is a rare disease and one of the thoughts is that it's very difficult to get PhRMA interested in rare diseases. But obviously if you've got three -

- there are three companies interested in pursuing this, there is some flexibility.

DR. BEAR: Yes. I mean, in some ways each company has a different story to tell. But, you know, the problem is that it is very expensive to develop drugs typically. Just the chemistry alone is very expensive.

And so mGluR5 was identified as an interesting target by big PhRMA 10 years ago as soon as the gene was cloned and a lot of money was spent developing drugs against that target with the idea of going into big indications like generalized anxiety disorder.

And a lot of the reasons that the big companies haven't been jumping in is because they don't want to "jeopardize" a big indication where they may see something -- some unusual signal may come up in a unusual disease.

So -- but there are other paths including, actually, there was a drug that was advanced as an anxiolytic and then abandoned

that was -- with a mechanism that was not known and then much later was discovered that as an mGluR5 antagonist so now that's a drug that is off patent and can be advanced in clinical trials. And that is one example of a path forward.

DR. LANDIS: So if you have a mechanism, then there may actually be really good candidates in the portfolios of PhRMA that can be retrieved and repurposed.

DR. BEAR: Yes.

CHAIRMAN INSEL: Mark, you said that -- it looks like from your diagram that maybe a third or 30 percent, 25 percent of kids with Fragile X have autism. Do we know what it is that is special about that group? And if you look at the mouse work that you've done with animals that have this Fmr deletion did they show -- did a third of them show social deficits or deficits that would be consistent?

DR. BEAR: That's a great

question, Tom. You know, one of the -- I think one of the answers -- without being an expert on this but one of the answers is the somewhat arbitrary cutoff. So I think that when I say, or when the clinicians that publish the paper say that 20 percent of the kids have autism, that is to say they satisfy the full diagnostic criteria for autism. Whereas the percentage of children with Fragile X that fall in the autism spectrum and have, you know, common phenotypes are probably a much greater fraction.

But to answer the question of what is responsible for the variation and severity of symptoms it would have to be other genes, genetic modifiers. And what we do know in the Fragile X mice is that different background strains -- the Fragile X mutation in different backgrounds strains will yield different outcomes.

For example, there's a guy at Baylor named Richard Paylor who is looking at

the effective background strain and has found some background strains that will show deficits in social behavior that are more autistic-like in the mouse than in some of the other more conventional genetic backgrounds.

CHAIRMAN INSEL: Do we have any evidence whether an mGluR5 antagonist would help on that dimension?

DR. BEAR: I think the jury is still out.

CHAIRMAN INSEL: All right. Other questions for Mark? Okay.

Peter, go ahead.

MR. BELL: What symptoms will you be targeting in the human population? In other words, if you give a patient who has Fragile X one of these mGluR5 antagonists, what do you think the outcome will be? What do you think you are actually going to change other than perhaps the kind of underlying biology of what is happening?

DR. BEAR: Right. No, that's a

great question because the devil is in the details. You may have a therapy that is actually very effective but you measured the wrong thing.

And so, I mean, this is outside my area of expertise but now that the prospect of therapeutics has emerged in a big way there is a lot of activity going on amongst clinicians to develop clinical endpoints that would be FDA approvable because in the end of the day that's what matters.

And so you can do -- we could do quantitative studies of things like, you know, startle, prepulse inhibition, things like that, eye blink conditioning, things that you can get a hard number, even galvanic skin response, things like that.

But those can give you data but they are not going to sway the FDA because it's not going to have an improvement of quality of life for the kids so there are going to have to be other endpoints like

irritability, aggression, and various scales like that. And so these are things that are active discussion right now.

And I think the, you know, the tragedy would be that we have a good drug but, you know, we run out of money before we measured the right thing, that kind of thing. But we have -- there are a lot of smart people working on it so I'm hopeful.

CHAIRMAN INSEL: Great. Thanks very much, Mark.

So we wanted you to also get updated by Walter Koroshetz from NINDS who organized a recent workshop on mitochondrial encephalopathies potential relationships to autism.

Walter, do you need to hook up a computer or are you good to go?

DR. KOROSHETZ: I'm set. I'm here to talk to people about a conference we held a couple of weeks ago at the end of the United Mitochondrial Disease Foundation meeting in

Indianapolis.

And so I want to tell you a little bit about what we know about the overlap between mitochondrial disorders and autism and then why it may be intriguing to look further. And it was an opportunity to bring together people who are experts in mitochondrial disorders with people who are experts in autism and have them listen to each other and exchange ideas. And hopefully that will also lead to a significant advance in the research.

Both conditions could certainly use better techniques, better treatments. And what we did is we got a number of experts from the mitochondrial field who had been at the meeting. Many people went to the meeting to learn more about mitochondrial disease.

Tom was there, Ed was there from CDC. And from the mitochondrial side we had Dr. Daryl DeVivo and Dr. Salvatore DiMauro who have been -- their whole careers have been in mitochondrial diseases. But they have also

seen a number of kids with autism over the years.

And then we had Dr. Robert Naviaux and Richard Haas from UCSD who are experts in mitochondrial disease but who have also seen a number of children with autism. And Dr. Bruce Cohen of Cleveland Clinic who is a mitochondrial expert.

And Doug Wallace who is a biologist who has been studying mitochondria most of his career and has made quite a few advances in the mitochondrial field over the years. And complementing that we had Dr. Pauline Filipek from UCSD where Doug Wallace is. She runs the autism service there, another pediatric neurologist who has also seen a number of kids with mitochondrial disease. And Joe Piven, a psychiatrist from UNC.

And then we had two people who were in the imaging field. We talked a little bit about imaging as a way of trying to tie

these things together, Kim Cecil from the University of Cincinnati who is a Ph.D. MR spectroscopist and Steve Dager from Washington University who is an imaging expert in autism.

And so Mark was telling you about how synaptic activity runs protein synthesis. Well, it turns out that the brain's synaptic activity is the major consumer of energy in the brain, energy being your ability to produce ATP which is the molecule, the coin of the realm in terms of energy.

So to do this kind of activity in the brain you need to develop energy and the main source of energy is the mitochondria. So the mitochondria are basically the power houses inside the cells. There is another way of getting energy but it's not as efficient called glycolysis.

The mitochondria are the main pathways to generate large amounts of energy, and they are also real important for maintaining cell health. They sequest the

calcium, the major storage points for calcium inside the cell. And they are also related to the process of cell death.

When mitochondria becomes sick they open up this pore. That's a sign to the cell it's time to cave in and the cell tends to go into apoptosis. So The mitochondria are really connected very heavily into this -- into all the major cell processes.

And the brain, since it is the most energetic organ in the body and needs most of the energy for synaptic activity, the mitochondria are probably really, really important for everything the brain is doing.

So, these are the people we talked about. And the agenda for the meeting, which is what I'll be talking about, is we had first a description of mitochondrial diseases, the genetics and the pathobiology. And unfortunately Mark made the story simple and I'm sure it's much more complicated. But this is such a complicated area I can't come close

to the level that -- what he got.

And the reason is because this is not a single gene disorder. This is a really complicated thing and we are trying to learn a little bit about that. Because I think we really need to know to understand what is out in the literature.

We talked about people getting together who have seen kids and done research in autism and mitochondrial function talking to each other. And then we spent a lot of time on the issue of how do you test for mitochondrial diseases because clearly if you want to look into autism we want to know if this is a problem so how are we going to find out and what tests are we going to do.

And there are pluses and minuses to the test. And unfortunately there are few -- there are very few kind of really definitive tests but there are a lot of other things to do that are kind of first steps but need to be refined.

Then we talked about research opportunities and challenges. And one of the things that, you know, we talk about is are the things in common and mitochondrial disorders are not uncommonly -- deterioration is triggered by something so the kids are -- sometimes are doing normally and all of a sudden, bang, they just get really sick and sometimes they die in a month or two.

And so something is triggered and the question is, you know, what do we know about those triggers and is there something in autism that is similar that causes clinical deterioration in autism.

So what are the potential ties? Now the evidence is there. It's not overwhelming that this is going to be the major answer to autism but natural fact since we haven't explored it all we don't really know what the extent of the involvement is.

I think it's pretty clear that the people around the table were convinced there

was a tie. There are certainly children who have a clinical syndrome that looks like autism that they believe have mitochondrial disorders. So that was not really debated. People really did agree on that -- the people who have seen kids.

And it comes from a couple of lines of evidence. One is that the people who have been seeing mitochondrial kids for a long time because they run in families, they will have -- they will be told, well you know, my other son has been diagnosed with autism. They bring him in and, sure enough, they think he has a mitochondrial disorder.

That is the link. They have been following families, these familial things so that that is one way in which this link has been made, families with no mitochondrial disorders that have children with autism and check do they have signs of mitochondrial dysfunction. Sometimes yes.

The complicated factor is that

even when we think you really have a mitochondrial disorder you sometimes can't even find it and that is actually the real problem that we're going to have going forward. And we'll talk about that some more why that is.

And then there are some children who have been described, as I mentioned, with autism spectrum disorders that have a mutation that affects mitochondrial function. And then the other thing that is going to be interesting is, as Mark said, there are a lot of genomic studies out there and they are now coming up with genes associated with autism and many of them are associated with activities. Some of them are associated with mitochondrial function. So those are the three major lines of evidence.

And there are a number of papers going back into the late '90s. These are just a couple that I took out. Pauline Filipek was there. She is the lady from University of

California Irvine. And she published two children with a 15q inverted duplication in the chromosome 15.

And these kids had respiratory chain abnormalities and we'll talk about what that means in their muscle. Hypotonia, moderate increased lactate. We'll talk about what that means in terms of mitochondrial function and motor delay.

And then there was a paper by Fillano showing patients with a particular syndrome of hypotonia, epilepsy, autism, and developmental delay which they named the HEADD syndrome, had respiratory chain abnormalities in the muscle and had deletions in the mitochondrial DNA.

There is another paper from Pons with three cases of a mutation known to cause MELAS which is mitochondrial encephalopathy, lactate acid, and stroke. It's a mitochondrial disorder. And they found three cases with this mutation in an affected

family. And one of these deteriorated after a viral infection which is pretty common to be said for the mitochondrial disorders.

The other thing about MELAS mutation is that it is now known that many people who have this mutation do not actually develop a disease syndrome so you can have the mutation and get by without disease which makes it interesting to look for in a population that otherwise doesn't fit the syndrome. Could it be -- could there be a form first of this disorder that is mimicking autism.

And there have been a couple of case reports of another mitochondrial mutation that is associated with mitochondrial disorder in muscle. And this one actually causes what is called Leigh's disease.

Leigh's is a very kind of aggressive mitochondrial disease that affects children usually around two years old, and high fatality rate over a year or two or so.

And they develop lesions in the brain that you can see on an MRI and pathology. And I'll show you what those look like.

But there was a child with that mutation who was diagnosed with autism and did not go on with -- but did have -- the putamenal lesion was in the sister so they both had the same mutation but it developed differently in the two sibs.

And then there=s another -- this is an interesting study which is the one -- the only one that actually looked at a population of people with autism it was done in Portugal in kids and they measured lactic acid in the blood and respiratory chain abnormalities. And they claim that about 5 percent of the people they started with have abnormal mitochondrial function.

The difficulties we'll talk about is that it=s basically their diagnosis was based on lactate and respiratory chain abnormalities. And those are problematic. I

mean they are interesting but there really can't be definitive at this point in time. That is the kind of evidence we are talking about.

And this is a kid, a four-year-old boy with a history of normal development until 18 months of age when he lost language, language comprehension, gradual increase in disruptive behavior, hyperkinesias, self-injurious behavior, clumsiness but no ataxia.

He had a normal plasma lactate but his sister has a mitochondrial disease, Leigh's disease, the one I mentioned which causes those holes in the putamen. So in fact, since he's biologically related to his sister, as I'll show you, he has to have the mutation, too.

This mutation for this is inherited through the mother. If they have the same mother, they are going to have the same mutation. She has Leigh's disease and he has the mutation but is presenting in a very

kind of like autism-like fashion.

And then this is going to -- I hate to get it too complicated but unfortunately this is the status of this problem. And it=s a nice -- this is an example from Dr. DeVivo of a family. So they are looking for the mutation and they find it in this person here.

This is the mother. The circle is the mother. They can't find it in this person here but then they find it in the kid here who has ADHD and a pervasive developmental delay as does his brother but they can't find the mutation in the brother.

So genetics says that this person had the mutation and they passed it here even though they can't find it and then it reappears here and they can find it with symptoms that are, you know, pervasive developmental delay and the brother has it as well but they can't find the mutation. So that now explains why this is complicated.

But this is the kind of thing we are up against.

And then the other part is this idea of will the whole genome association studies find genes that are associated with mitochondrial dysfunction. And there is one out in the literature now that is an aspartate/glutamate carrier and that is an important carrier protein to get energetic coins of the realm into the mitochondria so that it can lead to energy synthesis.

So that is one suggestion that if this is real, it could be working through a mitochondrial function. And I think there is a lot -- there will be a lot more work coming out on other genes, particularly the mitochondrial genes and we'll get to that.

So basically, just to summarize what I'm saying, at this point in time -- one of the -- Richard Haas basically put this slide together. In their thinking you have autism spectrum disorder which has varied

phenotypes. You have some kind of pure autism in the middle.

You have definite mitochondrial disease and there are these cases that I mentioned and maybe a few more where there is an overlap between autism spectrum, maybe even autism where you can say definitely there was mitochondrial disease.

Then there is this other question of cases where, you know, maybe the diagnosis of mitochondrial disease is not that secure and it=s called probable. And actually in the world of mitochondrial disease even kids who have, you know, severe problems with their muscle and their brain and their nerves, they still have to go with this diagnosis of definite, probable, or possibly because the evidence is just hard to nail down in making many of these diagnoses.

And for instance, the study by the Portugal group with the lactate and the respiratory abnormalities would be in this

possible group where there may be a five percent overlap. So our job is really to see how big these circles really overlap over the next couple of years and also try to get more towards the definites and out of the possibles.

So hopefully what I did now is get you interested in mitochondrial disease because it is -- I think it -- there is evidence it=s related to autism. We don't know how big it is but it is a pathway that is worth taking. So hopefully that will keep you interested in the next part which is trying to tell you about mitochondrial diseases and mitochondria.

So very interesting thing. With the mitochondrial actually a little bacteria remains in your cell so they have actually their own protein synthesis. They have their own gene which is a mitochondrial gene that is actually a remnant of bacterial genes that came in with, when some way -- I don=t know

millions or billions of years ago. Bacteria actually grew symbiotically in eukaryotic cells so that's interesting.

And so there are many mitochondria in a cell and the neuron where you have a lot of activity going on for senopia they are chocked full of mitochondria. Because that is where you need your energy function.

There are actually many mitochondrial DNA molecules in one mitochondria and there are many metabolic pathways which go on in the mitochondria and I'll show you those. You don't have to memorize them.

And there are about 1,400 proteins in a mitochondria but of those proteins only 13 are left encoded by that ancient bacterial genome. All the other proteins have moved and are now being controlled by the nucleus which is interesting but also adds this complexity because if it was just the mitochondrial genome we only have 13 proteins and we can

nail that down very quickly.

The trouble is that the majority of the proteins are being regulated out of the nucleus so now we are kind of back to square one in terms of we don't have an advantage of just looking at this small mitochondrial DNA. We have to also think about the nuclear genes that are then encoding for proteins in the mitochondria. So you have to worry about those two parts.

The interesting thing about the mitochondrial DNA is that the ones that are left over in the mitochondria are all in what is called the respiratory chain and I'll show you what that is. The respiratory chain, Doug Wallace said, is kind of like the electrical wiring in your house and that doesn't change.

His point is that the cell does not want somebody to mess around with the wiring. You can build a different kind of house, a southern style house, a northern style house but the wiring has got to work so

you've got to put the wiring in and not mess with it.

That is why he thinks that what is left being coded by the mitochondrial DNA is something you don't want to have any kind of recombination events going on in the nucleus. That is kind of a protected environment inside the mitochondria to serve for these three proteins and they are the real important proteins because they are the ones that are going to generate the ATP. The nuclear DNA codes all the other proteins.

Now, we're talking about mitochondrial DNA. The other fascinating thing is that it's not nuclear. When the cell divides the nucleus divides. You give half your genes, your husband gives half the genes to the kids. Here basically the ovum gives the mitochondria and that's it.

All the mitochondrial DNA is inherited from the mother. None of the mitochondrial DNA comes from the father. It

makes, therefore, for an interesting way of looking at inheritance of mitochondrial DNA mutations because they are all going to be inherited through the mother. And I=ll show you, actually you actually saw one, I'll show you again how that works.

The nuclear DNA will deal with genetics just like everything else so this is what you have to memorize -- I mean, just look at. This is the mitochondria and also a little bacteria. This is where the energy is coming in. The glucose, the sugar, broken down to pyruvate and then it can be -- it can go to lactate or alanine or it can go into the mitochondria.

When the mitochondria are bad then these things are going to back up and glycolysis is going to be turned on so you will see increased alanine, increased pyruvate, and increased lactate. If things are working well the glucose comes in here and basically the pyruvate comes in.

Basically what it's doing is it's going through this cycle called the citric acid cycle and it is generating these molecules which can then donate electrons to the respiratory chain. The respiratory chain of those enzymes I told you that are conserved in terms of the mitochondrial DNA and they are the ones that generate the ATP.

The glucose comes into here, the pyruvate into the mitochondria, electrons come off and they go from one chain to the other chain to the other chain and then finally come to the last chain in the electron. From oxygen is then, comes into like a motor almost that creates a membrane potential that allows ATP to be produced. This is your ATP manufacturing system here.

I mentioned there is a pore in the mitochondria. When this pore opens cytochrome c can come out of the mitochondria and give the signal for the cell to die. Basically the process of generating these electrons, the

electrons are actually coming from oxygen.

Oxygen and glucose are combining here to give you the energy and the electrons are coming from oxygen. Some of the electrons go in and they combine and give you ATP. There are occasional electrons that escape and those are called free radicals. The electrons escape from oxygen are free radicals and they can be damaging to cells or damaging to mitochondria.

That is the other thing that the mitochondria, especially in degenerative diseases, there is a big emphasis of whether free radical production in sick mitochondria is leading to neuronal death over time. That is something we're testing in Parkinson's and Huntington's disease right now.

In terms of mitochondrial disease the entrance is not entirely known. We don't actually have large population studies. The diagnosis, as I'll show you, is usually developed by applying a family history,

clinical examination, biochemical studies, pathological studies, and molecular studies.

Some of these biochemical studies vary from lab to lab which is a major concern in trying to do a scientific study. You are going to get a different result depending on what lab you are going to use. That is one big problem we're going to have to work on is standardizing these respiratory chain enzyme analyses.

The diagnosis, as I already mentioned, is usually qualified based on the strength of the evidence as definite, probable, and possible and there are basically schemas for doing this. It's much easier to diagnose than it is to exclude.

Fifty percent of the mitochondrial disorders present before age five. Mortality in childhood onset is 10 to 50 percent but there is a great heterogeneity in the causes and the course of the diseases.

One thing about mitochondrial

diseases that are known is that they often times will affect multiple organ systems so one thing that these mitochondrial doctors get is cases that no one else can figure out. The kidneys are involved, the liver is involved, the heart is involved, the brain is involved.

What's the diagnosis? That is often times a tip off because the mitochondria are important to so many tissues that if there is multi-system trouble mitochondrial disorders are often -- are sometimes at the rudimentary cause.

Lactic acid. As I showed you on that first diagram when the pyruvate can't get in you have a build-up of lactic acid so that is often times a screening test to look for high plasma or CSF lactic acid. The trouble is it's not sensitive or specific. If you ran around the block, you would have a high lactic acid. If you have a kid who is struggling when somebody is trying to draw blood, he'll have a high lactic acid.

As a matter of fact, when you draw blood for lactic acid you shouldn't even put a tourniquet on because just the ischemia from the tourniquet will increase the lactic acid. You have to be really careful in all these measurements that we are going to be talking about, how you actually collect them.

It is often used as a screening tool not specific. Sometimes there are kids who have it at one point in time with mitochondrial disease and then it goes away and then it comes back again. The time of when you draw it also seems to be important.

This is not, again, anything to memorize but it's basically how the mitochondrial disease people make their diagnosis. They have these lists of tests, lactic acid, amino acids like alanine. I showed you organic acids that come off the acid cycle when it's locked, CSF lactate and pyruvate.

Muscle studies will show you more

muscle study than DNA. They have different sensitivities and specificities and different validities. Except for the known mutations that are known to be associated with the disease, a lot of these other ones are evidence that add on on top but you need a whole bunch of things to be able to make the diagnosis. These are the kind of tests that the mitochondrial disease people talked about at the conference.

This is pretty definitive. This is the hole in the putamen that kids with Leigh's disease have. Unfortunately this kid died as many kids with Leigh's disease do. This is just an example of kids with Leigh's disease.

There are actually three different types of abnormalities that have been shown to cause Leigh's disease. You can see here these are all the symptoms these kids will have but it's a different percentage with each of the different causes.

Here we go to the mitochondrial gene. As I mentioned, the mitochondrial DNA is circular, it=s inside the mitochondria and encodes for these 13 proteins, 37 genes. The nuclear DNA for the mitochondria is thought to be about 1,500 although it's not clear for sure.

Leigh's disease, for instance, these are the different points of different mutations that have been associated with disease and Leigh's disease was here. Actually there are a number of different mutations along here that will give you Leigh's.

This is what I talked about, maternal inheritance. You have here a DNA type B. This mother has it so all of her children have it. This mother gives it to all her children, this mother gives it to her children. This was a boy. He marries this woman and she gives her mitochondrial DNA, which is type C, to these children. That is

an example of how mitochondrial maternal inheritance goes with mitochondrial DNA.

The other thing to note is that type A, B, and C here are actually related to ancestry. You can actually -- the mitochondrial DNA have been used to trace ancestry out of Africa different populations. One error has been that people have seen mutations, thought to be mutations, and they are not really mutations. They are just indicators that the person came from Finland or Asia or something. You have to be real careful.

Interestingly with the mitochondrial mutations that the site of these racial mutations are actually in fairly conserved regions which is quite surprising. Dr. Wallace says that the reason is that the mitochondria actually generate heat.

Depending on where you live in your environment you have to actually change the wiring diagram to generate a lot of heat

or less heat. That may be one of the explanations for why these areas are in conserved regions but they are really racially related.

The other part of the mitochondrial story which we have to talk about is this part which is called heteroplasmy. I mentioned that the mitochondrial get in the ovum and they will give you the DNA for the child. When the cells in the fetus start to replicate, the DNA will start moving into one cell or the other so at the end all cells don't have the same complement of the mitochondrial DNA.

Here is an example where there are mutations in two of the mitochondrial DNA in this mother's egg but then in the different tissues in the child here this one actually ended up with none of those mutations. This one ended up with 80 percent of its DNA being mutated.

That is because the mitochondria

are just going to start moving and your cell divides, then you don't get a mutation mitochondria. All the cells that come out from that cell are fine and will not be affected.

But if you happen to get most of the mitochondrial mutant DNA, then the cells that replicate after that will carry those. The problem here is you get very -- the genetics is tissue-specific.

We showed you that diagram before where they found mutations in this grandmother but only in one percent of the hair cells. Here in the boy, a grandchild, the mutations make up 3 percent of the mitochondrial DNA in the blood, 10 percent in the urine, 14 percent in the cheek cells, and three to 10 percent in the hair cells.

In this kid who has problems and definitely has this abnormal mitochondrial DNA from the grandmother, they can't find any abnormalities in blood, urine, cheek, or hair.

That doesn't mean it's not in a brain area involved in autism. That's the problem.

Unless you can know what the brain area is that is involved in autism is to get in there and see. You can't actually refute the idea that there is a mitochondrial problem. For this heteroplasty, this problem with the mitochondrial mutations being tissue-specific is a real challenge.

You actually have to collect a lot of tissue to try and get at your answer which is not a lot of fun for little kids when people start taking tissue from them. That's the kind of bind we are going to be in when we start to look at kids with mitochondria disorders.

There are a number of -- we talked about nuclear. We talked about mitochondrial problems. There are also some acquired conditions that caused severe mitochondrial problems. Reye=s Syndrome is thought to be a loss of mitochondrial function after an

infection. Maybe some interaction with aspirin.

MPTP which causes Parkinson's. The drug that people were using which causes Parkinsonism, that actually causes mitochondria and there are a couple of others out there in the world. 3-NPA which was eaten in China on moldy hay that caused necrosis of the basal ganglia. It's a toxin.

AZT is a drug for AIDS. Actually aging may be the thing that stresses mitochondria most. If you look at the aging brain, mutations seem to accumulate with age in cells that aren't dividing.

This is the muscle. What you see when the muscle is abnormal you see the accumulation of mitochondria on the outside of the muscle. These are eventually called ragged red fibers but basically when the muscle cell is not getting enough energy because of bad mitochondria, it replicates the mitochondria and they build up.

These are the kind of schema that the mitochondrial disease people use. If they have a kid they really think has it and they can't get an easy answer, they have a whole spectrum of things that they do to try and get answers. Basically at Columbia what they say is they bring the kid into the OR and put them under anesthesia and they do the muscle biopsy, they do the spinal fluid tap, and they take them and put them in a MRI scanner. These are the kind of things you can't -- you really almost have to have anesthesia to do. What anesthesia does to them is another story.

This is an example of the imaging which is interesting but, again, complicated. This is a child with MELAS syndrome -- that's probably not a child -- person with MELAS syndrome and with MRI you can actually get chemical spectra out of the brain.

What you see in the abnormal case when you have a symptomatic person is a high lactic acid in the brain in the ventricle.

That's the ventricle and that is the brain substance both with high lactic acid.

Then look what happens in a person who is asymptomatic. You don't really see that. You have to actually -- you have to actually time the scan when the patient is symptomatic to catch this in kids with mitochondrial diseases. You can see lactate on the brain which would be potentially interesting if you knew how to time it right.

In terms of things that trigger mitochondrial diseases, seizures are common for mitochondrial disease that affect the brain. Very common. Seizures will increase the energy demand to the brain so it is probably once they start to have seizures things will really go down hill quickly in mitochondrial disease.

That also occurs in 50 percent of autism kids, seizures. They are usually a bit more aggressive in kids with mitochondrial disease. Infections usually three or four

days after onset, they note kids get bad after the flu or measles or another viral infection. Some of that may be due to the fact of the fever. Heat is being generated by the mitochondria so the mitochondria are really moving quickly to generate heat in the case of a fever. Cytokines that come with infection are thought to affect mitochondrial function. Also to complicate things, the kids are not eating and drinking so they are not getting energy to their mitochondria and that is also supposed to be a stressor. Long plane rides maybe, low oxygen tension or the dehydration that comes in an airplane. There are some drugs that actually do inhibit mitochondrial function. Valproic acid is a common anti-convulsant and a mitochondrial disorder with that causes almost lethal hepatic failure. Tetracycline, sacromycin, erythromycin, AIDS drugs and aminoglycocides are others.

In summary we have lots of heterogeneity both phenotypic and genotypic.

We have organ-specific sites which are influenced by the mitochondrial mutation abundance. We have the concept of threshold. You need a certain amount of mutation load to cause the cell dysfunction.

We have different tissues with different amounts of mutations and also different tissues have different cellular energy requirements. These are all going to affect the phenotype and why it is so variable.

There are a lot of neuro-behavorial symptoms in many of the kids and adults but not all with mitochondrial diseases. Many of them do not look at all like what we expect. Some of the really severe kids have muscle trouble and neuropathy. There is some sense that autism spectrum disorder may be enriched in families with mitochondrial disease so is there form first out there with a mitochondrial defect that is really the way of autism.

How do we go about that? There are two main classes. One is a targeted approach. I mentioned all the kind of invasive things that they have to do to really go after a mitochondrial disease kid and that may be one way that we have to do that. We can't do that with everybody. You have to really pick a group.

Perhaps those that have the things that a lot of mitochondrial disorder kids have, hypotonia, epilepsy, developmental delay and a family history. You select a patient group and really go intensively after them. It's fairly invasive and would certainly take a huge amount of commitment on the part of the parents to allow their kids to go through something like this.

The other way is to do -- what has been out there and maybe do it better is the survey approach. We are doing tests now that are in those columns that are not very sensitive and not very specific. They give

you a sense of maybe what is out there but you can't really take it as a definitive answer so looking at lactate, amino acids, carnitine, acyl carnitine and ammonia.

You would have to look at the whole group and see if it looks like there is a pattern. Then maybe those are the people you go after more invasively. There are some ways of looking at the mitochondrial mutations that are not that hard.

The cells that come out in the urine usually have a high load of mitochondrial mutation in kids with mitochondrial diseases, as high as the other cells. That may be something you could do that is easy as well. Cheek cells, you can also scrape the cheek and gets some cells and look for mitochondrial mutation in that tissue.

The big problems are there is no definitive marker for mitochondrial disease to help convince you. Basically to diagnose

mitochondrial kids you have evidence here, here, and here and you put it together and I think you've got them. That's the kind of medical decision-making.

The timing is going to be critical, as I mentioned. The signs of mitochondrial dysfunction are coming and going with symptoms often times. Then we have this big trouble with the variability and how you do this enzyme assay to look at the mitochondrial chain enzymes. It seems like clearly valid techniques. The question is on different labs getting different answers.

Frozen versus fresh tissue is a big question. Some people say the frozen you just can't use and you have to use fresh and that is why it's different. The collection methods will affect the results. If you draw a lactate is going to depend on the level of muscle activity, caloric intake, how the kid is struggling, other stresses, maybe anesthesia.

Then a control group is going to be important as you can imagine for these kind of studies. That is certainly not going to be easy, certainly for the more invasive way of getting in.

That is kind of a summary. Sorry if it was a little confusing but it is a little bit confusing. Although it does look like there is something there to kind of go after we have to be really careful. Hopefully the mitochondrial field will also advance and give us new technology techniques that we can use to look at mitochondria disorders. Thanks a lot.

CHAIRMAN INSEL: Great. Thank you, Walter.

Let's take a couple minutes for questions.

MS. REDWOOD: One of the areas that I didn't hear you mention was treatment. From what I have read in the literature is that often times supplementations like coQ10

and carnitine are beneficial.

What I find somewhat fascinating is that those types of treatments are some of the things that parents have been doing in children with autism for several years now and have found marked improvement by doing urinary organic acid testing and things along those lines and targeted supplementation.

If you could just speak a little bit about potential treatments if mitochondrial abnormality is identified in a child with autism.

DR. KOROSHETZ: Yes, that's important. We are certainly testing things like coQ and Huntington's and Parkinson's. I showed you the respiratory chain. coQ is what actually moves the electrons from one of the chain enzymes to the other that is actually in mitochondria. It has other functions.

Carnitine is basically the fatty acids are brought into the mitochondria on carnitine. The idea is loading up the cells

with carnitine and coQ will help the mitochondria function. There are a number of other different things that people have tried. Unfortunately in the mitochondrial disease world it is such a rare disorder and there are such ups and downs that there isn't actually randomized control data to say that these things work. Actually when they have done the randomized control studies they have been very small, underpowered and they haven't seen anything.

But, that being said, most of the doctors who take care of these kids do use supplements fairly aggressively but it's just really hard to know when they are going up and down that the supplement is what is causing them to get better or not. Most of the docs who take care of mitochondrial disorder kids do that.

The other things they do is they really prevent. Anytime they get a fever they get them hydrated and they try and get some

glucose in to try and prevent the calories from dropping, preventing dehydration. There would be -- there is a huge I think market, quote-unquote, for drugs that would improve mitochondrial function. There are a couple of companies trying to do that now.

MS. REDWOOD: Another thing that we've just heard throughout the autism community, and this hasn't really been documented in the literature yet, that there was some investigation in 30 children with regressive autism.

A very high percentage, I had heard 30, had the same sort of mitochondrial abnormalities as Hannah Poling did. These were not necessarily mitochondrial DNA but it was more linked to nuclear DNA abnormalities. Have you heard the same investigation and could you comment?

DR. KOROSHETZ: I think that we've it's coming out but I haven't seen it. Tom, have you?

CHAIRMAN INSEL: I think it was presented as an abstract at the meeting but it wasn't presented at the meeting that we were at.

DR. KOROSHETZ: Right. The abstract I know, so we are waiting to see. The only thing you have to be careful of is the respiratory chain test. They really need to be repeated, multiple labs, before you could be sure that was the problem. The DNA mutations that are associated with diseases, those are usually pretty well nailed down by now.

MS. REDWOOD: Okay. My very last question is with regard to vaccines being potential triggers for mitochondrial disorders either from the viral component of the vaccine or we know that metals, particularly mercury, are known as injurious to mitochondria. Could you comment a little bit on the Poling case and the potential link between vaccination triggering a mitochondrial injury.

DR. KOROSHETZ: The only thing I could say the people we had at the meeting took care of mitochondrial kids. For mitochondrial children there's maybe 20 doctors in the country that are experts. Most kids go to the 20 doctors so they have seen thousands.

One or two of them remembered a kid who may have gotten worse after a vaccine but they have seen lots get worse after infections, so they vaccinate kids with mitochondrial disorder so they have not seen any evidence that vaccines are making the kids with mitochondrial disorders worse. They think it is so important that these kids don't get infections that they recommend full vaccination to kids with mitochondrial diseases.

That is as far as we went with that with the chance they knew something else was going on, that they were changing their vaccination practice, but none of them are

doing that.

MS. REDWOOD: I also heard that in this one case of Hannah Poling that the mother actually has the exact same inherited mitochondrial abnormality as her daughter but the mother does not have mitochondrial disease.

DR. KOROSHETZ: I don't know the case that well. The other thing we've heard is that is actually not a mutation but it is a marker of Finnish inheritance. Remember I showed you these different mutations that are related to racial background so sometimes they are confused with actually mutations that cause disease.

Some of these mutations because people didn't know that are really just a marker of inheritance. I really do not know the details of the Poling case so I'm not the right person to talk to about that.

DR. LANDIS: So if you were to look right now, there is nothing that would be

useful as a screen right after birth or at the first well baby checkup or the second well baby checkup that would say this is potentially a child at risk for mitochondrial dysfunction except for family history?

DR. KOROSHETZ: As far as I know right now. I think the thing that can be definitive is if you nail a mutation down and you know it's highly penetrant and you can find that in a newborn so screening for a mutation that is strongly linked to disease could be one way of going.

The difficulty with -- the difference between this disease and Fragile X is that the mutation may not be in all the tissues so you could miss it by sampling the wrong tissue. Knowing what the right tissue is is a big problem.

CHAIRMAN INSEL: Ed, you were at the meeting. Anything you want to add?

DR. TREVATHAN: Yes. Just along the lines of what Story was mentioning, one of

the things that came up among those of us child neurologists in the group that were seeing patients and there was further discussion during the breaks in the hallways that these tests that people have used to help them as an indicator for whether a muscle biopsy, for example, should be done like serum lactate pyruvate, CSF lactate pyruvate and so forth.

Those tests and decisions about whether the clinical phenotype in those tests warrant a child having a muscle biopsy under anesthesia have been used in very different populations that are relatively small compared to the population of children with autism. One of the concerns that was raised is given which, as you mentioned, including the MRI data.

It can be very sensitive and not very specific. There is concern that if we are not careful there are going to be a lot of children having anesthesia and muscle biopsies

unnecessarily. At the same time people don't want to miss the diagnosis of mitochondrial disorders but we also don't want children having invasive procedures that have risks that are not beneficial to them.

I think right now one of the things that came up at the meeting as one of the things we really need, and this is maybe an example of how work in areas other than just purely autism but, for example, mitochondrial disorders, that one of the things we really need are better screening techniques.

Even before that some laboratory standards for doing some of these studies it came out these different laboratories, especially for some of the respiratory chain, oxidative phosphorylation studies, that the standards are dramatically different from one laboratory to another and there is not necessarily an agreement.

We need to have some better

laboratory standards and also indications for doing screening studies and then indications for doing muscle biopsies in these different populations. I think Richard Haas' paper that you showed helps a little bit with that but this is an area of significant need.

CHAIRMAN INSEL: Other questions? Story.

DR. LANDIS: Duane, there is a lot of interest that you've been spearheading on newborn screening. I'm wondering if there is anything in the panels you guys have been thinking about that would be informative here.

DR. ALEXANDER: Not yet, Story. We have been using various approaches to try and expand a number of disorders that we can test for with newborn screening. This group is not one that is generally included in these yet because it's tough.

We are working with a number of other disorders, one that you are particularly in, muscular atrophy. This is a different

category of disease. The mitochondrial disorders have not been among those that we have been considering. This may be a trigger that maybe we ought in the next solicitation that is due to come out next year try to include those.

CHAIRMAN INSEL: Can I ask either Walter or Story, the mitochondrial hypothesis about Alzheimer's, Parkinson's, Huntington's, ALS, virtually every neurodegenerative disorder that is around, has there ever been a way to pin that down?

I would be concerned if once again we start down this pathway now for autism, in the same way we've been down this path for many, many other disorders without turning much up. Can we learn anything from that that we ought to be aware of now?

DR. KOROSHETZ: I think there is pretty solid evidence that mitochondrial mutations are accumulating as you age and there is pretty good evidence that the healthy

mitochondria are related to the health of your cell.

In things like Parkinson's there is more and more circumstantial evidence that the mitochondrial abnormalities are what make that cell type. There is something peculiar about that cell type and the interaction between that cell type's environment with getting lots of dopamine which is actually a very big source of free radicals and mitochondria and they may play a role. There is evidence when you look at mutations that cause Parkinson's some of them do seem to go through a mitochondrial pathway. Richard Youle at the NIH intramural is looking at processing of mitochondria in the theory that the damaged mitochondria just are not going into the waste basket like they should in Parkinson's and that is what is causing trouble. Yesterday there was another company with another drug that they thought was affecting mitochondria that works in

Parkinson's models. I think we haven't been able to nail it but it's kind of the best stuff we have.

CHAIRMAN INSEL: It's just intriguing your comments together with what we heard from Mark because if really developmental synaptic plasticity is what is the convergent theory now for autism and this is a step that is essential for that to happen, it may provide a mechanism. I just am concerned since we've been down this road and so many other places. It's so tissue- and even cell-specific it's going to be really hard to nail down.

DR. LANDIS: I would say that mitochondria dysfunction has been a high -- has had high visibility as one of the causal factors in neurodegenerative disease for 20 years. More than 20 years. There is still no definitive proof, but we are running trials looking at coQ10 and creatine in the context of Parkinson's disease. Now, it's very

indirect and we'll have those results in --

CHAIRMAN INSEL: 2030. Anything else for Walter? If not, thank you, Walter. That was great.

Let's take a five-minute break and come back for public comments so just to stretch and then we'll get started in five minutes.

(Whereupon, the above-entitled matter went off the record at 2:47 p.m. and resumed at 2:53 p.m.)

CHAIRMAN INSEL: We've got public comments from several people. The first name on the list is Kelli Ann Davis. You can do it right here. That would be great. Again, because there are several people, we want to keep these relatively short if possible. I think you've got five minutes.

MS. DAVIS: Is it on? All right. My name is Kelli Ann Davis and I'm the D.C. political liaison for Generation Rescue. I'm going to be reading this quickly but I would

like to submit this letter into the record. This letter was issued to Secretary Leavitt yesterday by the Committee on Science and Technology from the Subcommittee on Investigations and Oversight.

Dear Secretary Leavitt, the Combating Autism Act of 2002 called upon the Department of Health and Human Services to establish an interagency autism coordinating committee. I understand that the IACC has been appointed and has begun work. A key task of that committee is to develop a strategic plan that will guide research investments.

In the Combating Autism Act Congress directed DHHS to conduct research into screening, diagnosis, treatment, and medical care for individuals with autism. These areas of research are essential to a balanced approach. In addition to these areas I strongly encourage the IACC to promote a balanced research portfolio when examining the underlying causes of autism spectrum disorder.

An examination of the fiscal year '07 ASD research portfolio shows a strong preference to fund genetic-based studies related to autism. There is growing evidence that suggest a wide range of conditions or environmental factors may play a role in the emergence of ASD.

The case of Hannah Poling is just one example that is suggestive of the very important lines of inquiry. It is becoming more clear that ASD is not a singular disorder but one with numerous and complex etiologies.

Research into the causes of autism need to examine and differentiate the numerous biomedical causes for the similar set of symptoms diagnosed as ASD. Without an understanding of the different biomedical causes for ASD it will be difficult to pinpoint a genetic link and equally as important to understand the role environment factors play in the emergence of autism.

Additionally, understanding the

different biomedical pathways will assist other branches of research including early diagnosis and potential treatments. On June 29, 2008, meeting in Indianapolis to examine the link between mitochondrial encephalopathies and autism was a promising start to a more nuanced examination into the causes of autism.

I hope that the research endorsed by the IACC would include work to further clarify these matters. This work seems so important that I would expect the Department to undertake these efforts even before an endorsement from the IACC.

Throughout the 1990s there was a dramatic increase in the number of children diagnosed with ASD. It is unlikely that this increase is entirely attributable to the more accurate and vigilant diagnosis of the disorder. During this time the public health agencies of the federal government were both slow to react to the increase and slow to

communicate effectively with the American public.

I am disturbed that efforts to undertake and dedicate resources towards competence of research into this disorder was largely forced on public health agencies by Congress and citizen activists. This delayed response has caused many Americans to distrust the Department of Health and Human Services when it comes to ASD.

Given the fact that the Department has lost much of the public's trust, it would be to your agency's advantage to involve as many people from the activist community as possible in any decision making process. If the Department of Health and Human Services is going to provide effective leadership in autism research, diagnosis and treatment, then you need to build new relationships and repair old ones.

I urge you to consider forming a secretarial level autism advisory board.

While the IACC is the primary mechanism for the coordination of research, surveillance and early detection activities within the Department of Health and Human Services an AAB could provide additional feedback and serve as a liaison between parents, individuals with ASD, advocacy groups, and the Department of Health and Human Services and would assist in reestablishing public confidence.

Such a board could be of whatever size and composition you found helpful and should include voices that can articulate the full range of views and concerns in the ASD community. Since research is a key area of discussion and dispute, it is prudent to include multiple research-oriented organizations on this board.

Groups such as SafeMinds, Generation Rescue, Autism Speaks, the Simons Institute, the National Autism Association, and the Autism Research Institute all have or are currently supporting research.

Such groups have experience evaluating research, an in-depth knowledge of the current body of ASD research, and an appreciation of the new questions that may need to be examined in order to move our understanding of ASD forward. Such a panel could provide an annual review of progress in autism work across the Department as well as work that is funded outside of official circles.

It would also provide you with a sounding board for departmental ideas on how best to proceed and to communicate with the public. The work of this board need not be duplicative of that of the IACC.

And probably one of the most important paragraphs. By this letter I would ask for your thoughts on forming an autism advisory board. Further, I would ask that you keep me informed of the work of the IACC from this point forward and please provide to my subcommittee a copy of the IACC's research

report when it is completed.

Please direct the report or any questions concerning my request to Dr. Dan Pierson or Ms. Heather Parsons. This letter was the result of a year-long Generation Rescue-led initiative in collaboration with SafeMinds. We are continuing to work with this subcommittee.

We worked very hard for the Combating Autism Act, for the language that was put in to the Combating Autism Act, for the language that specifically talks about research into the role of vaccines and that is exactly what we would like to see, the kind of research we would like to see done. Like I said, we will be working both with the Secretary's office, Dr. Rob, and also with Dan Pierson and the subcommittee. Thank you.

CHAIRMAN INSEL: Thank you.

Margaret Dunkle.

MS. DUNKLE: Good afternoon. My name is Margaret Dunkle. I'm a senior fellow

with the Center for Health Services Research and Policy at George Washington University. Some of you know me through my current work.

Some of you know me as recipient of the American Academy of Pediatrics' Dale Richmond Award for outstanding achievement in the field of child development. Some for the collaborative efforts I direct in Los Angeles County to ensure that all children receive good developmental screenings and effective follow-up.

More recently some of you have come to know me because my nephew is Dr. John Poling. John's daughter, Hannah, is a little nine-year-old girl from Athens, Georgia who is the subject of a case the government conceded in federal vaccine court.

The nine vaccines Hannah received in one day in July of 2000 significantly aggravated an underlying mitochondrial disorder she had which predisposed her to, in the eloquent words of the vaccine court, to

deficits in cellular energy metabolism and manifested as a regressive encephalopathy with features of autism spectrum disorder. In simple terms, Hannah has autism.

I believe in a strong and safe immunization program. Yet, every day more parents and some pediatricians reject the current vaccine schedule. Hannah's condition is not rare. Hannah's condition is not rare.

The best evidence strongly suggest that at least four to five percent, as you have just heard, and perhaps as many as 20 to 30 percent of children with autism have mitochondrial dysfunction as does Hannah. With one in every 150 children on the autism spectrum, these issues are urgent and they are important.

My recommendations today reflect the mission of this committee. Most importantly with Marshall Plan dispatch, the federal government should create a new, intense basic scientific research program to

get to the bottom of what is going on with the many Hannah Polings out there, focusing on the role of mitochondrial dysfunction and neural inflammation in not only autism but in many other disorders as well.

The research must be bold. It must go wherever the science takes it with no conditions and no sacred cows. Funding an estimated 200 million for starters must not be taken from the vaccine injury compensation program.

Two, quickly find ways to screen for and identify susceptible children, the subset of children like Hannah, for whom vaccines or another adverse event might cause or worsen mitochondrial dysfunction and lead to symptoms of autism.

Study siblings of children with autism to identify biomedical markers that could lead to prevention, screening tests and treatment and immediately create a database of these and other children with disabilities to

track adverse vaccine effects and establish tailored vaccine safety guidelines.

Three, piggyback new research efforts onto existing studies to answer important questions about autism, vaccines, mitochondrial dysfunction and neural inflammation. Test alternate vaccine schedules and frequencies through the National Children's Study. Use Duane's new federal Newborn Screening Saves Lives Act to propel advances concerning genetic and metabolic disorders.

Integrate new analyses into existing studies and cohorts of patients with known mitochondrial dysfunctions including those going on at Johns Hopkins University, the Cleveland Clinic Foundation, Columbia University, and elsewhere.

Number four, launch a nationwide initiative to spot children like Hannah who have any abrupt developmental regression including those that are vaccine-related and

speed them into intense early intervention which is already publicly funded through the Individuals with Disabilities Education Act including the Zero to Three Part C program.

Also, strengthen the vaccine adverse event reporting system known as VAARS so it actually does the job it was set up to do. And beef up VAARS so there are serious consequences for failure to report adverse reactions to vaccines.

Five, reform vaccine practices to ensure they are as safe as possible for both children in general and susceptible subgroups. Examine the number and frequency of vaccines, the use of combination vaccines, the preservatives used, and the ages administered and the developmental status of the children.

Six, update the vaccine injury compensation program. Allow families longer than three years to file so that parents can focus on early intervention, not legal paperwork. Update the vaccine injury table as

new discoveries about autism, mitochondrial dysfunction and immunological disorders emerge. And explore limiting VICP compensation to the most critical immunizations, returning adverse reactions to other vaccines to the regular court system.

Seven, improve federal oversight of vaccines. Consider establishing an independent agency analogous to the National Transportation Safety Board with sufficient clout and resources to enforce vaccine safety.

I am proud that my family is providing hope and voice to the many families across the country with their own Hannahs. I'm also proud of their leadership to nudge those of us who care about good public policy and good public health to do the right thing and to do it right.

A beautiful little redheaded girl has sounded a loud, profound wake-up call and raised tough and important questions. Your challenge as leaders concerned about autism is

to tackle these issues in a way that is effective and that is unflinching in response to Hannah's clear scribblings on the wall with clear advances in science and improvements in our immunization practices. Thank you.

CHAIRMAN INSEL: Thank you.

Jim Moody.

MR. MOODY: Thank you, Dr. Insel. I'm from SafeMinds as well as Director of the National Autism Association. Two letters are in your folder and in lieu of time I want to be brief and summarize a few key points.

One is we are very happy there is a general understanding of the need to put the budget analysis in as part of the strategic plan. But beyond just putting numbers to the research projects listed in the plan, we think it should also include a comprehensive cost-of-disease analysis. The annual cost of autism could be between 30 to 70 billion dollars or so. You have to figure out what autism cost society or what you should or

would be willing to spend as a society to treat existing cases and prevent new cases.

It might well be that three environmental studies isn't enough. It might be that the goal should be to define the environmental triggers and eliminate them even if it cost $500 million because society would benefit from such action. I think further work is needed there.

On the vaccine issue I would respectfully challenge IACC to do what must be done and include a specific plan in the strategic plan for vaccine research. Congress has asked for this. The community has asked for this both in public comments and at the town meeting and some of the GAP initiatives submitted this spring.

The science has not been done. The gold standard here is a comparison of the health outcomes of vaccinated versus unvaccinated children. Only then will we know for sure whether the cost of chronic disease

caused by a vaccine is in the same range or even perhaps greater than the cost of preventing infectious disease.

Parent's concerns are entirely rational and are growing. Until these questions can be answered, they will continue to grow.

It is an easy study to do. It can be done retrospectively with existing unvaccinated kids as controls. It could be done prospectively as part of post-market surveillance. This is not rocket science. It is simple epidemiology that needs to be done.

The Stratton Study, Stratton himself retracted a no-causation interpretation pediatrics letter in 2004. The IOM itself has recognized there is a genetic subpopulation that has not been adequately studied. These are open questions that need to be addressed.

The third thing, I would supplement the urgency point with a comment

that the strategic plan needs to come face to face and question are we facing a substantial rise, or a word often used in the community, an epidemic of new cases or whether most of the cases have always been here and we are just learning how to count them better.

The policy implications of confronting an epidemic are much different than confronting a background chronic disease that has always been here. The CDC is really quite good at confronting things like SARS and bird flu and salmonella and infested pet food. These were all epidemics that threatened the vitality of the United States and autism should be treated in the same way with the same sense of urgency.

Finally, funding process for re-engineering. Dr. Insel's comments on a movement toward RFAs and special emphasis panels we think are spot on. That would help ensure that the necessary research gets done in a focused and accountable manner rather

than relying on traditional RO1 mechanism used to fund really interesting basic science but not necessarily coordinated to achieve the particular results sought by Congress: prevention, treatment, and improvement for quality of life for those with autism.

I think some additional work needs to be done on the public participation side. That is another goal specifically allocated to IACC by CAA is to look at ways to improve public participation in decisions relating to autism. The DoD model is a good one. The people involved with the community that work on that program are very happy even though it's a very modest amount of money. Perhaps that money can increase but the lessons learned from the DoD program would provide a valuable insight into mechanisms that can be incorporated in the strategic plan.

The final point is that the strategic plan provides a wonderful opportunity to bring the discipline of the

strategic planning model to use the power of science to achieve the goals of determining cause, improving treatments, preventing autism and improving quality of life for those with autism. That is why so many people in the community are fighting so hard to get the best possible plan and the work of IACC toward that goal is much appreciated. Thank you.

CHAIRMAN INSEL: Thank you.

Scott Bono? Catherine Gottfred? Also not here.

Azik, any other comments? Okay. Anything else from the committee itself? Any other closing comments or remarks about the day? Plans? I think we're clear on -- that you are going to get more information from us on the revisions within the plan highlighting areas where you suggested, or the group has suggested, changes.

Della.

DR. HANN: You all are going to send your -- some of you have asked to send us

suggestions. If I could ask that you please do so within a week's time so that would be next Tuesday, that would be very helpful. Thank you.

CHAIRMAN INSEL: Anything else? Walter.

DR. KOROSHETZ: (Off mic.)

CHAIRMAN INSEL: Can we put that on the IACC website as well?

DR. HANN: We can link to it.

Walter, she didn't get that because it wasn't said into a microphone if you wouldn't mind just coming and saying it again, please.

DR. KOROSHETZ: I just said that the summary of the mitochondrial conference and autism will be on the NDS web and we can put it on the IACC web as well. We have DVDs so if people wanted them, we can make copies of DVDs. We taped the conference.

DR. LANDIS: So I guess one issue about -- because of compliance issues for

access, we can't post the slides from the meeting because they wouldn't be accessible to --

CHAIRMAN INSEL: Because of 508?

DR. LANDIS: Right.

CHAIRMAN INSEL: Okay.

DR. LANDIS: So that is part of the reason why the DVDs were made. This turns out to be a difficult issue any time you have a conference and people want to have the slides from the conference up.

In order to be able to do that there would have to be verbal descriptions created for each of the slides which isn't done most of the time, which means we are handicapped in how we can provide to the broader community the outcome of workshops like this.

CHAIRMAN INSEL: I hope that's clear. Good. Anything else? Thank you very much. A long day. I'm glad you stuck in there with us. I think we got a lot done but

we are not finished. We'll see everybody on November 21st for the next and final discussion about the plan.

(Whereupon, the above-entitled matter was concluded at 3:15 p.m.)