U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF MENTAL HEALTH

INTERAGENCY AUTISM COORDINATING COMMITTEE MEETING

MONDAY, MAY 16, 2005

The committee convened in Bethesda, Maryland at National Institutes of Health, 31 Center Drive, Building 31, in Conference Room 6C10, at 9:00a.m. Thomas Insel, M.D., *Chair*, presiding

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PROCEEDINGS:

Dr. Thomas Insel: Good morning. Normally we meet on Fridays. So it's a little out of kilter here to meet on a Monday, but welcome to everyone. And thanks for those of you who have traveled from afar.

I am Tom Insel, Chair of the Interagency Autism Coordinating Committee. And, as always, we will start with the round of introductions. We will start from my left.

Dr. Sue Swedo: Good morning. I'm Sue Swedo from the NIMH.

Dr. Jose Cordero: Good morning, Jose Cordero from CDC.

Dr. Audrey Penn: Audrey Penn from NINDS.

Mr. Jon Shestack: Jon Shestack from Cure Autism Now and the parent of a son with autism.

Dr. Merle McPherson: Merle McPherson from HRSA.

Mr. Lee Grossman: Hi. I'm Lee Grossman. I'm President of the Autism Society of America and the father of a child with autism. Forgive me. I'm going to take just 30 seconds here just to

acknowledge the many people from ASA that are here, particularly the Chair of the ASA Board, Dr. Cathy Pratt.

Dr. Kathryn Carbone: Kathryn Carbone, FDA.

Dr. Barry Gordon: Barry Gordon, Johns Hopkins, but here in my capacity I think as the parent of an autistic child.

Dr. Lu Zeph: Lu Zeph, University of Maine Center for Community Inclusion in Disability Studies, the University Center for Excellence in Developmental Disabilities at the University of Maine, and also guardian of a young man who is now 32 with autism.

Ms. Margaret Schaefer: Margaret Schaefer, Administration on Developmental Disabilities.

Dr. Judith Cooper: Judith Cooper, NIDCD.

Dr. Cindy Lawler: Cindy Lawler, NIEHS.

Mr. Jim Hanson: Jim Hanson, NICHD.

Dr. Alice Kau: Alice Kau, NICHD.

Dr. Ann Wagner: Ann Wagner, NIMH.

Dr. Insel: Very good. Welcome to all of you. We've got quite a full agenda. So it's going to be important for us to stay on schedule. We've

promised Merle McPherson that she can leave at 11:00. She has a very important role here today. So I want to make sure that we're able to get most of the introductory remarks and some of the progress notes out before we move to the Services Subcommittee's report, which is very important for us.

I thought what we would do for an initial session is what we have done in the past, and that is to take you through a very quick overview on some recent developments and to do this quite broadly. So we won't say very much about any of them specifically, but I wanted to make sure that, most of all, we have a chance to feature two developments from the broad autism community to hear about the Autism Treatment Network as well as Autism Speaks, two efforts that have really emerged since our last meeting in November.

Now, those of you who are on the Coordinating Committee would know that much of what we try to do from the research perspective has been guided by a strategic plan, which we call the Research Matrix, that was put together in 2003. And I will

just start my remarks by just giving you an update of where we are with that matrix because it does provide for us a framework of where the priorities need to be, at least from our perspective.

This was the result of a great deal of work from a group of experts who came in originally in the summer of 2003. So it's been almost two years since this process actually got started.

It was the request of a House and Senate conference committee that asked that we put this together and report back to them on an annual basis, which we have been doing since.

As you will recall if you are on the Committee, this group put together a fairly elaborate plan that would go over ten years. And they brought it to us at the November 2003 meeting for approval. There was some discussion of it. We decided to march forward. And we are now at the 18-month phase or about a year and a half in.

Now, you can't read this, but you have a copy of it in your book. It's just to remind you what we talked about at that point, which was that we divided up the targets for research into short-

term, medium-term, and long-term, also into low-risk, medium-risk, and high-risk over here. So these up here in the upper right-hand corner represent the seven to ten-year high-risk goals. These represent the one to three-year short-term goals or low-risk goals.

And so essentially what we want to talk about here is, given that we've got a total of about 15 targets for these first 3 years and we are a year and a half in, how are we doing? How far are we along in this process? And what can we point to as having accomplished in this first 18 months?

Again, you'll have copies of this in your notes, but I thought I would just highlight a few of the areas that we have made some progress on so you can hear about what we're trying to do but to recognize also that there's an awfully long way to go on almost all of these measures.

One of the most high-risk short-term goals was to develop a biomarker, a peripheral biomarker, for autism. And I would love to tell you that we have that now. There certainly is a lot of work going on in two NIEHS centers funded in both

Sacramento and one at Rutgers in New Jersey, but we have got a ways to go here.

I think, even with the best technology, we are finding that biomarkers are going to be more difficult than what many people had thought maybe two or three years ago.

There was a report out of the M.I.N.D. Institute at IMFAR the week before last that suggested that using a high throughput proteomics approach that was developed by Seramed, a biotech company out of California. I think they had 70 children with autism and 30 or 40 control kids.

It turns out that there were some striking differences. There were about 100 proteins that separated out the autistic sample from the control sample. This is, again, very early, and it is going to require a lot more work to refine this, but it does provide some evidence that there may be an opportunity here for coming up with a diagnostic test.

Of course, the question would be since these were children in the four to six-year age range who had been diagnosed and treated for some time,

it would be really interesting to see whether this will transfer to children at risk at a much earlier stage. And that's part of what that group is hoping to do now.

The other striking thing that came out of that effort was that there were some differences in immune cells that were really unexpected. There is about a 40 percent increase in NK cells, about a 20 percent increase in the B cells in the autistic sample, so raising a question about whether we ought to be again focusing on some autoimmune mechanisms for the etiology or pathophysiology of autism.

Another item up here is looking at the efficacy of established treatments for the -- let's see if I can even find this -- for pharmacological, behavioral, and other treatments that target symptoms associated with autism. Again, there's lots going on there.

The STAART centers have several trials, including a multi-site citalopram study that is underway. As you I think know -- you have heard about this at a previous meeting -- there is the

trial of early intervention and behavioral intervention that Geri Dawson is championing at UW as well as a similar study at Rochester.

UCLA has a program on social skills training. There is a placebo-controlled study of gluten-free, casein-free diets at Rochester. So I've got a number of projects underway but too early to actually take any of that to the bank. We're still a ways from having the results.

In terms of infrastructure, this is really for genotype/phenotype studies. These are the kinds of things that I think all of us thought were probably most critical to do in these first three years. I'd say we are making some progress here.

There's a genetics initiative, which had already been -- we already had the repository. There's a new initiative out to try to do fine mapping based on that repository. That RFA has been out for a few months. We've got a number of outstanding applications in, just about to schedule the review. And I think we will be able to push that forward very quickly over the next few months.

You also hear something about a national database that is going to be presented later this morning, which is an attempt to be able to, again, build this infrastructure for informatics that we think is going to be critical for having the kind of national approach to understanding autism better.

Just a few other things to mention here. Existing data study to begin to characterize the autism phenome as part of a phenome project. There is, in fact, a phenome project that has been launched at the M.I.N.D. Institute. There are plans to develop a kind of East Coast version of this within our intramural program here at NIH. And this is something that we consider really a high priority and something that needs to move forward rather quickly.

Infrastructure; enhanced brain acquisition. We're up to 88 brains. They have been distributed to 42 projects. Again, that's been the project that was funded. I think you might have heard about that at the previous meeting. So we've got, again, lots of traction in this area but maybe not

going quite as quickly as any of us would have hoped.

Multi-site imaging. I'm not going to go into this in great detail except to mention that we have already collected about 500 scans as part of a large multi-institute project. It's a multi-spectral study.

So it's not just MRI but also DTI and a number of other techniques to provide a good sort of controlled database or a good set of normative scans with which the nation can have this basically as a sort of database repository that one can then go after for individual studies of autism.

We're not yet at the point where that is public. It should be within I think this next year. We do have about 1,000 structural scans that are available that were done through the intramural program here again in a control, large control, population.

And we think for this purpose the first step really has to be to have those maps of development of the healthy brain before we march ahead to

begin to ask what is happening in cohorts of children with autism.

There are some neuroimaging committees for both the STAART and CPEA centers. And we can talk more about that in the discussion if you like.

The last thing to mention here is it says here "Twin resource developed to study heritability and environmental factors." There are studies now underway, both at UCLA and in Wisconsin, with a twin resource. So that has moved forward.

There are lots of areas that we wish we had done more on and that we are going to have to push more aggressively in these next few months if we are going to meet the three-year goal that we have from the matrix.

As it says here, "Randomized clinical trials developed for the evaluation of effectiveness of early behavioral interventions and factors predicting response to the intervention." That's clearly something we need to move along. It's got to be a very high priority.

Outcome measures improved. We have got a process underway to begin to use the Web state of

the science message for looking at all of these outcome measures. Ann Wagner has been pulling that together for psychosocial treatments. This is again, I think, a great opportunity to partner with ATN and others as we begin to look at what are the best measures for monitoring outcome.

It says here, "Research Communication Network." And you will hear more about that, I hope, in a few minutes from both Autism Speaks and the Autism Treatment Network. That really seems to me to be a great opportunity for a collaborative effort.

And then just a few other places here. "Effective interventions expanded, disseminated, and implemented to improve outcomes in the school and community settings."

We are going to be hearing more about that when we talk about the Services Subcommittee. And we have a chance to look at the progress that they have made. The hope is that we will actually have a parallel matrix with a set of very urgent milestones for services as well, which can interface with this research effort.

Just to note a few recent developments that are mostly to be talked about later in the course of the day, but in case there are things that you are particularly interested in hearing about, I just thought I would feature them because these have all come up since our last meeting.

We have now launched an intramural autism research program under the leadership of Sue Swedo, who is here. This is going to be in the NIMH intramural program. And it's an opportunity for us to do some kinds of research that are unlikely to be funded through the extramural peer review mechanism.

There is an RFA that will be coming out very soon for Centers of Excellence. As you know, the CPEAs and the STAART centers will be reaching the end of this cycle fairly soon. In going forward, we thought that, rather than having two independent centers' mechanisms for autism, it made sense now to merge these and to have one program for Centers of Excellence.

So the RFA has been put together. We are looking forward to getting that finalized in the

next few weeks. But I think that this is going to be, again, an important stimulus for the next five years as we think about what needs to get accomplished in this area.

The CDC Autism Awareness Campaign was launched I believe at the end of February or early March. And that is something that hopefully Dr. Cordero can tell us a bit more about in terms of where that sits currently and what the initial outcomes have been.

And then what I most of all wanted you to hear about this morning -- and I thought I would actually cede my time to some guests that we have with us -- are two new efforts: the Autism Treatment Network and Autism Speaks, which are in some ways the new kids on the block and ones that we feel are really, really promising for the kinds of items that are in the matrix.

Recall that when the conferees requested this matrix effort, they specified that this was to be thought about as a public-private partnership effort, that there were items in this matrix that would require help from the private sector and

some that might be done best within the private sector. And the hope was that we would build the kinds of relationships that would deliver for children and families with autism without so much attention to who was doing it or necessarily even how it was getting done.

So with that as an introduction, I thought it would make sense for us to hear from both the folks of the Autism Treatment Network as well as Gary Goldstein, who is here, and Alison Singer from Autism Speaks.

Before I turn the mike over to Richard Fade, any questions about these initial comments?

Mr. Shestack: Yes. Tom, this is Jon Shestack.

Dr. Insel: Yes?

Mr. Shestack: A couple of quick questions. One, is there a dollar amount out of intramural that is part of the commitment to the phenome project and/or a dollar amount intramurally in the intramural program to autism in general?

And could you explain a little bit more in-depth what the folding of the STAART centers and the CPEA centers into one program means, and

particularly what it means in terms of like a net dollar amount spent on autism?

Dr. Insel: Right. So let me answer the second question first and then I'm going to turn the first question over to Sue Swedo, who is much closer to the intramural effort.

The plan for the centers would be to take the current budgets, which are roughly $22 million that are going into the combination of CPEA and STAART, and make that the base out of which to build a new center mechanism.

For us, the issue is also what those centers should look like. The hope would be, rather than just creating the current centers, that we would develop centers that would potentially be able to do some different kinds of things. We have talked quite a bit about -- they will probably be called ACE centers, Autism Centers of Excellence.

One thought would be that there could be both the sort of classic center mechanisms that we have now as well as using some piece of this for a research network and to have more of what you could call almost a virtual center across various

sites, particularly for clinical trials, but also even for other kinds of research; for instance, if we decided to really build a proteomics approach, where you would acquire samples from multiple centers rather quickly. So that's a somewhat different vision going forward, but we're still crafting that. And it will be important to get input from people around the table as well.

Sue, do you want to speak a little bit about the intramural program?

Dr. Swedo: Yes. It's not possible to answer the specific question about dollars. I can tell you that we have 12 staff members now dedicated to this project, many of whom are still to be hired, but we're quickly doing that.

We envision launching two major characterization studies. One is, as Tom mentioned, the East Coast version of the phenome pilot. And, as some of you know, the M.I.N.D. Institute is devoting many of their resources to getting that done at UC-Davis. And we will be recruiting a comparable number of people, trying to get 55 subjects in this first year to determine

feasibility and validity of the measures that the phenome has devised.

The second characterization or phenome study is actually for regressive autism. Building on my work in obsessive compulsive disorder and looking at immunologic subtypes of OCD, we will be looking at regressive autism to determine if some of those kids have immune deficiencies.

And to do that, we're collaborating with Cliff Lane and Mike Sneller in the National Institute of Allergy and Infectious Disease, NIAID. So we're very excited about that immunologic collaboration. I think it is really first-rate.

Then we envisioned launching three treatment trials over the next six months, two of them the summer and the third one probably later in the fall. The first treatment trial is a glutamate antagonist riluzole, which has been used with some success in obsessive compulsive disorder. We envision using that in grade school-aged children who have severe stereotypies and anxiety behaviors.

The second one is actually assuming that we'll

have positive results from the immunophenotyping, and we'll determine that we'll use an immunomodulatory agent there.

And then the third one is actually modeling the children with autism as a subgroup of them having severe anxiety disorder because so many of them start having symptoms at the point that separation anxiety develops. We are hypothesizing that it's pathological anxiety. And we'll be doing a combination of anxiolytics and intensive behavior therapy as early as possible for those kids.

Those are the first five studies. We actually have also talked about trying to do intramural testing of some of the standard therapies used by many families. And probably at the top of that list is chelation.

Dr. Insel: One of the great opportunities with the intramural program is to move quickly as new opportunities arise. And it's almost an ideal place to do this kind of work for a problem like the problems of autism, where you may want to bring in patients from anywhere in the country

where we're able to do that here at NIH; where you may want to have the most high-tech research tools, we have those, particularly for imaging and immune studies and proteomics and all of that; and where you want to be able to move without having to write a grant and go through peer review and the many months that it takes to get funded because we can move as quickly as an IRB can move to be able to do a new clinical study.

So it really is we think an important new part of the effort to try to make a difference here, but we need to get the people on the ground. And we need to get this group actually launched over the next few months. We're really delighted, though, that Sue has taken this on.

It's very hard to put dollar figures on this because in the intramural program, so many of the dollars are embedded. You don't charge for travel. You don't charge for salaries. You don't charge for patient care. All of the care is free. It is all within a research context.

So it's always complicated whenever we try to compare an investment intramurally with an

investment extramurally. We try, but the numbers are very soft.

Are there any other comments? If not --

Mr. Grossman: Tom?

Dr. Insel: Yes? Go ahead.

Mr. Grossman: I have two questions. So here we are halfway through the first three years of the research matrix. How would you rate our progress at this point? And those areas where we're falling behind, can you detail why we are behind? Is it because the goals were too aggressive, perhaps, or lack of resources?

Dr. Insel: That's a great question. I mean, I think I could give us a grade, but it would in some ways be more interesting I think to get a grade from this Committee or people who are on the front lines to look at this and say, "Are we really keeping up? Are we moving as quickly as we should? Should we be doing better?"

It's no question that there are some places that have been disappointing. From my perspective, we would have liked to have had a treatment network going in the way that we do for other

disorders, where we could quickly move with new interventions, the kinds of things that Sue was just talking about where there are some ideas out there that we haven't had a platform on which to move them through quickly.

I think that the whole idea of getting the phenome done, understanding the various subtypes of this disorder, are going to be really critical. I think all of us realize now that we should be talking about autisms, not autism. Yet, we are not sure how to do that.

We're not sure what the boundaries are, what the subtypes are. And that is going to be for us, I think, a critical goal for these first three years if we're able to meet the four to six-year mark because it's getting into that middle phase when you really need to have the fine grain analysis of which treatment for which child. And we're not there yet.

I think the place where we have made the most progress is in the early intervention side, being able to come up with tools that do allow us to do early detection. That's perhaps the most promising

piece of this. And that is the part that may have the largest public health benefit.

Those are just my off-the-cuff picture or evaluation of this. What really counts is what all of you think about how we are doing. Does anyone else, Barry or anyone, want to respond to this?

Dr. Gordon: I would like to just say that one of the ways of evaluation progress, though, is against the enormity of the problem. And one of the typical problems in science is you appreciate the problem is more difficult than you thought it was initially.

So, you know, as a parent, I'm upset at the lack of progress in a number of areas; in particular, the lack of progress in translating known treatment modalities into actual application for all children who need them and all young adults who need them.

In terms of the science, I'm holding my breath because some of these recent developments are very exciting. But in other areas, we have had issues where similarly exciting developments have not panned out. And so I certainly would love to see

the basic science pursued with great vigor, and it is being done.

So I am both encouraged and discouraged at the same time. So I would give it mixed marks right now for the whole effort. But, on the other hand, it proved to be a very, very big problem.

You know, I remember similarly about 15 years ago some people were predicting Alzheimer's disease was going to be cured in 10 years. And before that, I think 20 years ago, they were predicting it was going to be cured in 10 years. So, you know, there have been other examples where the benchmarks have to be adjusted, too.

Dr. Insel: I guess I should add that for this early phase, a lot of what was required is putting together the kind of infrastructure you need to make progress. And the database still needs to be done, but that is going to be an important piece, having the networks in place, having the tissue repositories, both genes and brains. All of that is part of what we really need to do in the first three years. And we are making some progress there. But, again, it's not as fast as one would

like.

Dr. Gordon: Just one other comment that from the standpoint of a clinician as well, having NIH being able to do intramural studies, targeted treatment studies, is a tremendous advantage since it can call on the entire United States for subjects that institutions and other groups really can't do.

So I think that is going to be a tremendous advantage to solve, hopefully solve, an approach, targeted problems quickly, get them done and move on, unlike the situation we have had for a number of years where problems have kind of sloshed around, never being quite solved to anybody's satisfaction because no one can pick up enough patients in the right kind of study design to answer the questions that people inevitably have. So that is very encouraging.

Dr. Insel: Jon, I'll let you have the last word.

Mr. Shestack: It's not a word. It's just a question. You know the advocacy groups worked hard to get the STAART centers off the ground. And one

of the things we were hoping that they would provide was a mechanism for clinical trials or for information to be shared through a network.

But it sounds like you're saying that that has not been that effective and you have to revamp the program in order to make that more effective. Is that correct?

Dr. Insel: It hasn't done everything we wanted. The clinical trials have been slow. The database piece you'll hear about later this morning. We have sort of another generation of that coming along, which we think will be more effective.

But this is a field, I have to say, that in some ways is not where the Alzheimer's field was ten years ago. This is a field that still has to be built. We're still getting the people in and the infrastructure in place. So it is not surprising that it would take longer than this first, two or three years to really ramp things up. We still don't have some of the fundamentals here that you have for juvenile diabetes or cystic fibrosis or other disorders.

I want to make sure that we have a chance to hear from both Autism Speaks and the Autism Treatment Network. I would like to turn this over to Richard Fade. Richard is the father of a ten-year-old child with autism. He recently retired as a senior vice president of Microsoft and presently works in a venture capital firm.

Richard and Susan have been active in promoting services and interventions in autism since 1999. In 2000, they created this endowment, which established the Autism Center at the University of Washington, serves on the board of that autism center and the Northwest Autism Foundation.

Along with partners from the foundation, Mass General Hospital, and physicians from six other hospitals, the Fades have helped found the Autism Treatment Network, a network of institutions focused on improving the standard of care for those with autism in the United States. Richard recently also joined the board of Cure Autism Now as part of a strategic alliance established between CAN and the ATN.

So, Richard, if I can have you come up here? I think your slides are up. Once they're turned on, we are ready to go.

Mr. Fade: Great. Thank you very much.

The last time I was here I think I had a hard time just driving the mouse. So hopefully it's a low bar for a better performance on my part.

Thank you, Dr. Insel. Good morning, members of the Committee, ladies and gentlemen. We appreciate the opportunity to update you on the work of the Autism Treatment Network.

When we were last here, it was September of 2003 and you had just completed the matrix that Dr. Insel was just referring to. It was just being presented for approval. And I would not like to hazard a grade on our own performance at ATN, much less the performance against your goals in that matrix.

Suffice it to say we have come a long, long way in 18 months to define our goals and objectives and to begin to move on the action necessary to realize those goals.

One of the members of the Committee, Dr.

Gordon, you know, in my closing comments pointed out the complexity of the task that we were setting about to undertake. I remember that very well. That comment has come back to me many, many times in the ensuing months. But I'm happy to say I believe we have made some really dramatic progress.

With me today is also Dr. James Perrin, who is the Director of our Coordinating Center at Mass General Hospital. He will be sharing some specifics of what we are actually doing in the centers and in the practice that we are pursuing.

Since we were here last, I have to concur. I believe there has been some progress in the field of autism. For example, in early diagnosis, in early intervention, I think understanding and actually accomplishing early diagnosis and understanding the value of early intervention, I think that situation has improved a great deal since we were here in the Fall of 2003.

We are impatient to see similar gains in the area of treatment. And I'm so gratified to hear the comments, the opening comments this morning

that people understand that there is really, you know, a great opportunity in this area.

So it's not really surprising that our goals in creating the ATN are really to establish a national nonprofit organization that is focused on creating a network of hospitals and physicians to focus on the study and advancement of treating individuals with autism.

This slide was designed to be more of a leave behind, so I'm not going to read you every bullet point on the page. But suffice it to say our focus, you know, the thing that stands apart from what we are doing, from what has been done is it's a collaborative approach.

It spans multiple existing centers that are seeing patients with autism today. And we're focused on treatment, on sharing information on outcomes, on better capturing the data of the health issues of these individuals with autism, and sharing that information in an iterative way.

Today the ATN is comprised of six institutions with what I will call varying degrees of expertise. And we are really literally a coalition

of the skilled and the willing.

When you are trying to get an organization like this off the ground, both of those are obviously very important. I mention this because our vision is really greater than a network of six to ten centers, but for the next year, we see our size being limited primarily as a function of funding and also our desire to get our initial work done in creating the tools in our process in the network with a much smaller group of institutions. Dr. Perrin will talk a bit more about that work in detail.

So clearly our vision, this bottom bullet point, really is about being able to begin to publish articles on treatment, to evolve treatment guidelines, and to be the credible good science, good medicine, if you will, organization that parents and primary care physicians can reference when looking to treatment for their loved one.

So why did we create the ATN in the first place? We were created out of the desire to accelerate advances in treatment and in treating autism because, of course, in our opinion, it is

moving just much too slowly.

Being the father of a child with autism, it is just shocking to me the state of and the progress that is being made in treating this disease or disorder. We don't even really know as a group how to talk about autism effectively.

So, you know, if you look across this first set of bullet points, it is really about to begin to understand this because today we have really weak insights into the overall health issues of individuals with autism.

I'm so, so gratified to hear the comments of the speakers prior and the discussion around the table about the immune system possibilities and the observation of the differences in the autistic population in terms of various proteins or anomalies that they have. We just really don't understand the breadth of the health issues in autism.

When I was here before, I was very quick to point out we in our organization aren't proposing that these health issues are directly in line in some causal link with the cognitive or other

neurodevelopment issues in autism. They may just be coexisting features.

But we do observe when a child has autism, that child comes into a physician's office, they present as a collection of symptoms. And today many of the symptoms are being associated with autism. Some physicians in our network today are finding, "Hey, that is just not true."

Some of these symptoms we are able to treat and ameliorate. And the child still has autism, but they are far healthier and they are more successful in their educational programs.

So basically this first experience is that experience shows dramatic progress is possible for a very large group of kids, sadly, not all kids today with autism, but for a very large group of kids, and that, in fact, we believe that though the entire field of autism research is woefully under-funded, then, in particular, treatment is terribly under-funded and has lacked focus in recent history especially.

The next fourth and fifth bullet point on this slide, the promising practice exists in silos and

the great controversy over health issues, effective treatment, these are sort of two different sides of the same coin.

We have physicians in our network that are achieving, actually, some pretty dramatic gains in the patient population. But, yet, you know, their work is very controversial. There is no vehicle to prove out their work in a very disciplined and good science way. And as a result of that, you know, we remain in the same turmoil that, for example, children's cancer was in 20 to 30 years ago.

If you had a child diagnosed with leukemia 20 to 30 years ago, you came to my hometown to Fred Hutch, you would get one set of treatment protocols. If you went to M. D. Anderson in Houston, you would get another. Children died at a horrendous rate compared to today because we didn't understand, we didn't have a collaboration on outcomes, and we didn't really know how best to treat this disease.

So most of you know that story. They banded together a group of institutions that shared

information on the outcome that in an iterative way shared the information on their intervention. And they have all far better treatment for cancer. So today if you have a child with leukemia, seven to as many as eight out of ten kids actually survive and go on to remission.

So we are not pioneers in this work. We are inspired by the work of the Cystic Fibrosis Foundation and models like the Children's Cancer Network. The fundamental "Aha!" for us is that what is missing in autism is a vehicle, is a framework to engage, is a set of tools and support and leadership to unite a group of institutions to share information in this way.

And though the very specific initial areas that we have chosen to work on that Dr. Perrin will share with you to explore, if you will -- and he will talk about them -- they may or may not yield dramatic results for the patient population.

But for me, the home run in creating the Autism Treatment Network is actually establishing the framework and getting this feedback loop going amongst the institutions, because if these do not

prove to be significant improvements or provide significant improvements in the field of autism treatment, you know, we have the means in place to explore the next intriguing side of findings that will.

So as I put in this bottom bullet point, this sounds very cliché, but I believe what we are doing in the ATN is very transformational work. I believe we can fundamentally enhance and accelerate. And we can provide the quality of treatment for autism in the United States. And we can provide a framework that greatly accelerates getting this done.

And I think we can do this. I think this work is pivotal. I think it is as important as finding the funding. Just pouring more money on singular institutional research I don't think is going to get the job done in as effective a fashion. And I don't think that we can reach out and touch the lives and improve the lives of as many people as we can in putting together something like the ATN.

So I put this slide in primarily just to give you some idea of what's this going to cost, what

is the reality of actually doing this. You know, we all have ideas we can share with each other. We have passion about this thing. But the reality is without money, none of this is going to go forward.

So part of the vision for the ATN was to begin with centers that are already seeing patients that have reasonably large patient populations and flows of patients through their institution today.

What we are doing initially is adding significant new practices and costs to their model. We are bringing specialists into their practice that, frankly, in many cases don't exist today. For many of these centers, their interventions are largely behavioral and educational, and we are for the first time bringing some more standardized and deeper medical review and diagnosis to that practice.

So to establish the core of what we are doing for the first three years, it's going to cost a minimum of about $10 million. And this is just based on the notion of six centers. So if we add more centers, this cost obviously goes up.

It's ironic I heard the term "public-private partnership" mentioned before. We totally have seen this from the beginning. It is that kind of effort. And our strategy has been really to provide the leadership and to build the initial work of the ATN on the back of private money, on donations and private funding, including the founders and then a number of other organizations.

We recently entered in in February to a strategic alliance with Cure Autism Now. They're stepping up to help us with a significant portion of our funding. But, really, the magnitude of what we need to do is not secured. And we will be working this year to complete the necessary pledges and funding.

And we are reaching out to you, those of you here in this room who have the capacity to work with us. And we ask you to think about the work of the ATN and where we could work together and where you could support our work and help us, including funding.

So I have just a very high-level set of bullet points I am going to use to talk about our goals

for this calendar year. And then I am going to ask Dr. Perrin to take the lectern and actually drill down on some of the work we are actually doing inside the network.

So initially we had to get the institutions who are participating established and introduce the Autism Treatment Network. We did that at the beginning of the year.

Largely what we have been doing, we have been a core group of about 20 to 25 physicians who met every 3 months for the last 18 months. This group has been very focused on a discussion of establishing a common multi-disciplinary practice across their centers, including a common work-up and a snapshot, if you will, of the health issues for the patients coming in to the centers.

So a big part of this is to agree on the practice requirements and the tools. And, of course, as I mentioned before, these centers, the six of them, are all over the map in terms of readiness and, you know, for the work today.

But we're establishing a common set of requirements. The centers are putting together a

proposal to establish that common practice by the end of this calendar year. And as a result of that, they will begin to receive funding against those goals.

So we will also, one other big milestone for us this year, hold our first physicians' conference -- Dr. Perrin will talk a bit about that -- in Chicago in September of this year, but it will be our means to begin to communicate broadly -- it's a physicians' conference, it's not a parents' conference -- to communicate broadly what physicians in our network are finding and our intent on evolving these practices forward.

So the rest of the bullet points on this slide are really about the work that myself and others need to do in working with you. With the other organizations, by the way, I should say if we are the new kid on the block, I feel pretty tired and old to be that entity.

We have also a great relationship with the Autism Society of America. We enjoy the support of Cure Autism Now. We are engaging with Autism Speaks. And I expect we will spend some more time

with NAAR as well.

So we believe our work is actually a work that every advocacy organization would naturally want to support. And we see ourselves, if you will, as a coalescing force in the community on that point.

So now what I would like to do is conclude my comments and ask Dr. Perrin to join me here at the lectern and talk a bit more in terms of specifics of what we are doing, the initial areas we have chosen to work on. Please give him your attention.

Dr. Perrin: Thank you, Richard.

What we have really done -- I would like to spend just a few minutes telling you what we have accomplished so far in terms of what we think to be the goals for the next year, but very much we are very interested in your ideas and advice in what we are doing and where we might take it.

We have really achieved agreements with six major centers for this multi-disciplinary collaboration. Those agreements include what they are doing about finding appropriate space and clinical staffing for their work. We are working very actively to finalize, which we hope to do in

the next few weeks, sort of our research database protocol, a fairly complex database protocol.

Again, as you are developing the phenome project activities, we ought to be thinking about how those interact with what we are trying to do there as well.

We have an agreement with a leading data epidemiology group that is going to help collaborate with us in the development of the ATN and also all of the staff training and related issues there.

So our key activities for this year are really to finalize the clinical assessment protocol. Within that, given some of the interests of our groups, we will have standard protocols for the assessments of three sets of conditions associated with autism: gastrointestinal manifestations of autism or of other diseases within autism, metabolic conditions that may be associated with autism, and some of the issues relating to sleep.

Some of the initial goals we have are using the database we will develop to determine the prevalence of these three conditions in autism and

the related conditions.

We, as Richard said, are having a conference in September on emerging practices. And our first sort of associational study given the database we are developing is the association of GI symptoms with self-injurious behavior in children with autism.

The clinical assessment protocol, we think that following the developing of the core research protocol, which is something we plan to have done by June that the clinical committee will also review and agree on a common clinical assessment in all sites for all children.

In other words, as we get started on the research side of the endeavor, we are going to be introducing a relatively small number of children into the research protocols, partly to get ourselves up to speed and capable of doing it, but we plan to expand that quite dramatically pretty quickly in the context of the ATN.

And we would expect that over time, in fact, all children in these sites will get the same assessment protocol, rather than a group that is

for the research base and another group that is for the non-research base. And, as I said before, we are actually already developing and have almost finalized standard protocols in these three areas.

We are going to look at the prevalence of GI conditions, metabolic indicators and conditions, and sleep conditions using the initial ATN database to determine these. Again, our system, our standard assessment protocol, is very carefully designed and will allow us to do this fairly quickly is our first set of activities.

The conference in September is called "Emerging Practices in the Care of Children and Youth with Autism." Our focus this year will be on the assessment of these three areas that we have particular initial interest in. And we do intend to publish the papers arising from the conference in the clinical journal to get the word out and to get some permanence of the kind of work that we are doing.

I would love to have your ideas on this sort of first associational study. Our pain symptoms indicated in children associated with self-

injurious behaviors, are they really associated with increased rates or some rates of gastrointestinal disorders in children?

So we will use the initial database that we are developing. We will be able to gather information on self-injurious behavior, both from the ADI and ADOS but also from another much more intensive measure of self-injurious behavior. We do have a fairly comprehensive series of GI symptomatology from the GI standard protocol that we have.

If we find anything, this will allow us to really support some more active search in the future for GI conditions, learn more about how to identify these effectively, figure out which children need some attention and some interventions, which need more complex interventions than this simple definition of symptomatology, which ones need scoping, which need other kinds of treatment for inflammatory disease, et cetera.

Our three-year goals are some continued learning from this multi-disciplinary clinical

collaboration. We have actually already found, by the way, that clinicians in this group from meeting for years are starting to recognize that things they never thought about in managing children with autism are things they are now routinely doing. Or they might never have thought about the fact that this is a sleep condition that might merit some attention, rather than simply being a sleep condition that it must just be her autism, or similar things around gastrointestinal symptomatology. We're really finding already changes in people's practices.

Part of what we have done in establishing this network is to get collaboration within these institutions of clinicians who had not necessarily ever talked with each other before about the fact that, in fact, there may be some gastrointestinal issues going on in children with autism that need some thoughtful scientific base of attention.

We will have, within three years' time, a very large population of very well-characterized children and youth with autism. And that will allow us to carry out, again in collaboration with

folks here, flexible and efficient studies of new treatment for autism in a much more speedy way than we have been able to do up to this point.

Let me turn this back to Richard for the last few comments. And then we will get some questions.

Mr. Fade: Yes. It dawned on me as I was listening to myself and Dr. Perrin present, you know, when you think about autism, you think about what are the mainstays of treating autism today. They are behavioral and educational programs. So where is all of that, Richard, in your plan?

The reality of the situation is that one day our vision could be broad enough to encompass also behavioral and educational programs, but, at least today, parents and practitioners have some choices, some very solid choices that they can choose from in terms of what to pursue in helping an individual with autism in the area of educational and behavioral programs.

Our observation in founding the ATN was that there was virtually a vacuum in the area of medical issues and that, worse, in the parent community, some of the next set of things that you

as a parent encounter are just a dramatic increase in the amount of information in the field of what I will call alternative medicine or medicine that has not been well-founded, in fact, or researched. So you're besieged by all of this information. You really don't have anything to reference.

I go back to that comment about complexity. You know, we do understand the complexity involved in autism. It is a very complex matter. You know, the truth of the matter is that complexity falls on the shoulders of parents to try to sort out every day. Parents are ill-equipped educationally, financially, emotionally to do that.

And, you know, we understand it's complex, but we can't let that defeat us. We understand that there is a way forward by establishing a model like this and by beginning to explore some of the more promising areas, some of which that we have listed here in the prior slides.

These topics, by the way, were surfaced primarily looking at the practice of participating, the physicians participating in our network, and also just a whole list of what I will

call smoke out there in the community, where there is really a great need to qualify and understand and separate fact from fiction.

So why create the ATN? We just think this dedicated and iterative approach is really a model whose time has come for our community. It has been used with great success in other diseases.

Collaboration trumps stand-alone investment. I think we are learning that over and over again. And we believe that, even in just beginning through the emerging practices conference this fall to share best practices and to be a credible organization that primary care physicians can reference with confidence that we can really begin to impact literally tens of thousands, perhaps hundreds of thousands of people's lives by providing that kind of thought leadership.

So this is sort of the thought that I will leave you with. I was interested and intrigued when you were asking about where we were in the matrix. But in the area of treatment, if we don't coalesce this kind of focused network, this iterative sharing of outcomes and sharing of

information, where will we be five years from now?

You know, I think it is, and I may be straying into treacherous waters by saying this, but it's not clear that medicine or research arrives at a point where collaboration is natural without the benefit of an organization like this to stimulate that.

I mentioned that. I see some smiles around the table, but the currency of the community is really about credit and being recognized individually or the institution funding follows that credit. So unless you have an organization that galvanizes collaboration, supports it, provides it the tools and the framework and leadership, I think we really miss a great opportunity.

So, with that, I would like to stop my comments, I think, and ask Dr. Perrin to join me back up here. I apologize. I think we have run over about three or four minutes in our comments.

Tom, should we take questions, Dr. Insel?

Dr. Insel: Yes. Go ahead. Thanks very much for that presentation. We are open for questions and comments. Barry?

Dr. Gordon: I think it is fantastic what you are doing. I have thousands of potential questions, but in the interest of time, I want to limit it maybe to one or two big ones. Is this being done as an add-on to clinical efforts or are you also planning that this will be a true research program where people will have to give separate consent to be part of it? And I ask that, in part, both because of the issues of how universal this gets applied because research always has problems with gaps in data and clinical research has tremendous problems with that, but also because of the issue of how you are actually going to pursue some of these questions to make them not just correlational attempts, not just descriptive, but maybe actual experimental interventional attempts to solve some of these problems.

Dr. Perrin: Yes. I think you're right on target about issues that we are going to be addressing. I mean, you know, the optimal circumstance would be where all kids at least meeting basic criteria in all of the centers that

we are working with would be entered into research protocols and would get the same base of care across the country. If you think about what we did, in fact, with children with malignancies, that is basically what happened.

Every child who met criteria was basically enrolled. There is essentially no child in America who is not on a research protocol if she has a malignancy. And we would see a very similar kind of process here if we can work it out.

Now, of course, lives are different today with IRBs than they were 25 years ago and all of the issues involved with that, but that would be the goal, in fact, to have a consistent pattern of care that every child gets and that every child would also be enrolled in a very flexible research network that would allow us to study treatments.

You know, I realize we are starting with associational studies. We have got to start somewhere and make sure that our systems will work. We realize the difficulties with that. We would like to move quickly from associational studies to doing something different for young

people.

Mr. Fade: Other questions?

Dr. Insel: Jose?

Dr. Cordero: Thank you for a great presentation. I think that the idea of sort of the cancer networks and especially the history of what happens with children with childhood malignancies is just a great story.

One of the key factors, then, of success there was the early recognition of children with malignancies so treatment could be started early. And that is also a recurrent theme with autism. We don't have data for autism in particular but overall for developmental disabilities, about half the children that get diagnosed are recognized at age five. How do you see in the ATN working in the early recognition so then the treatments can start early?

Mr. Fade: Yes. You know, I think we are going to draft on the good work such that you have started in this past year and of the advocacy organizations that are supporting and your partners, for example, the early signs and those

kinds of things.

And the reason I mention that is, one thing I have learned in my history -- I am not in medicine. I am not a researcher. In my history, you have to focus to be successful.

So today the problem in the centers that are participating, it isn't an absence of patience. And, thankfully, from the time that my son was diagnosed -- he's now ten. I think the average age of discovery for a family was somewhere around three, three and a half.

In my observation, what we are seeing in the University of Washington, you know, the good news is I think we are down by about a year. I think it's really happening, at least for us in Seattle, to be more like about 2 years of age and sometimes 18 months, which is tremendously positive.

So right now we have more of a yield management problem than a recruiting problem, if you will, you know, in our center. So we probably won't devote much of our time specifically on that.

We're trying to do the bit once we've got them

in the clinic, how do we most effectively treat them? How do we share information? How do the good practices at Mass General become quickly understood in Seattle and Baylor, at Cleveland Clinic and the other institutions?

I don't know. In the appendix, I put the participating institutions and some other information. So you can reference that to the slides. But basically we probably won't address that. I think there was one other question.

Dr. Insel: Lucille?

Mr. Fade: Yes.

Dr. Zeph: Thank you. This is a wonderful addition. I see it as a real complementary piece to the work that we have been doing in terms of early identification. I hope that you will in the very least introduce the concept of early identification in terms of -- and spread the word with the medical community, first thing. So thank you for that.

The second is I wonder why if you -- I noticed that there was nothing about neuroimaging in there except maybe as it pertains to sleep. And I wonder

what the reason is for that or if you have thought about where that might play in, particularly around the issues of seizures and the complications that happen as a result of that.

Dr. Perrin: That's a really very helpful question. I think at this point, in fact, the groups that have been thinking about what our database and common practices would be have struggled a good deal in thinking about what would be routine imaging to be done. And the sort of sense is probably not to include routine neuroimaging.

But we are trying to now develop some sort of branch points that would describe children for whom neuroimaging makes most sense and figure what they are. We are very much at that point in our database development.

Dr. Insel: There's one question from the floor. You will need to come to a microphone for us to be able to record this. Go ahead with the follow-up.

Dr. Zeph: The other question I had is your target audience in terms of physicians, whether or

not you are looking at only pediatricians or if you are looking at across the family practice and other GP groups that see a large percentage of the children and the youth. One of the big problems that we have is that we focus in the developmental disabilities on the pediatricians and then, as we know, people grow up. And it becomes an issue.

Dr. Perrin: I think two things to say. This conference we're running in September is really for clinicians. I mean, Richard says physicians, but I keep telling him it is really clinicians who are actively involved in the care of young people with autism. That's the target for that particular set of activities.

On the other hand, I mean, the broader agenda is, in fact, to influence what happens in the primary care network. And a number of us are pretty actively involved in a number of organized medical groups, the Academy of Pediatrics and others, and really intend to bring the lessons that we can and have some experience in doing that and making them effective, not only within pediatrics but, of course, family practice and

other places, too. So I think that's clearly part of our agenda.

Dr. Zeph: I just want to thank you for the work that you're doing. The fact that there has not been a medical protocol for health care -- and I would love the word "health" somewhere in your acronym because I think that health and wellness for this population of individuals is critical to the quality of their life. That's it.

Mr. Fade: Thank you. We agree. And I think you and I -- actually, our acronym is sort of misguided and misrepresentative, but, you know, it can only be so many words long. So we'll stick with this one for now.

There's one more question. There's a big flashing stop sign up here. So do you want to take this question?

Dr. Insel: Let's take the last question. And then we want to move on to hear from Dr. Goldstein.

Dr. Becker: I'm Kevin Becker for the National Institute on Aging. In your three research interest areas, is there any interest in immune or

autoimmune processes and how flexible?

You know, if you get ingrained in those three research areas, you're going to fund it and stuff, but how flexible are you in that as these maybe later-breaking genetics and proteomic data comes out?

Dr. Perrin: I think that the initial work is guided by two or three things. One is a number of clinical experiences that our clinicians have had and families have had, which have really indicated there may be something really beneficial in understanding more about these three areas. That's sort of guiding us.

I think our long-term view is very much that if, for example, the autoimmune stuff, which a number of our folks in our own institution are quite interested in, really plays out to be far more productive and leads to opportunities for interventions, we are very much involved with wanting to make that happen.

Dr. Insel: Last question. In looking at what you're doing, if there is another institution that wants to become a seventh or eighth or ninth

institution, is that in the plans?

Mr. Fade: Yes, absolutely. That's what I was trying to say. Our vision really for this thing is to be much broader than just the six to ten. I mean, we would like to see an ATN practicing center in every what I call NFL city in the United States such that, you know, defines sort of an obvious distribution that is relative to population. So it's a good proxy.

You know, today it is really about funding. And, actually, in this next year, as we develop these tools, it's about the desire to keep the group initially fairly manageable I'll call, you know, while we get the basics of the database flushed out and some of this work done.

There's one parting point I'd like to make, and it stems on your question, which is, we love basic science research. We think it is important. We are not proposing our work as an exception to that. We are proposing our work in addition to that.

And our dream, our hope is, that if there was some promising work that came out of systems

biology or any other discipline or research out of the matrix, today we wouldn't have a competent network to drop that work into to validate it and to accelerate its availability in the public more broadly. So we think we are a natural complement to the more basic science research, and that is what we are trying to do.

You know, the example I use in my business, you know, in finance is, you know, I feel like we have a disproportionate amount of our investment in start-up companies. And we are really the blue chip income sort of part of the portfolio that is missing today.

The good news is you can hit a home run with a start-up company, but an awful lot of them never see the light of day, right? So we want to establish that iterative infrastructure and just move down the field by a series of doubles and singles. How many metaphors can I mix here in closing?

[Laughter]

Mr. Fade: Thank you very much. You have been very kind. We appreciate your support.

Dr. Insel: Thank you, Richard. That was terrific.

[Applause]

Dr. Insel: Well, it's great to see this kind of progress in terms of pulling groups together and the possibility of a collaborative effort that may be much greater than any one institution could possibly pull off. And it's wonderful that a group of entrepreneurs like Richard and others have begun to make this happen.

The other example of this, which we're going to hear about now, is Autism Speaks, which is a new organization that Gary Goldstein will talk to us about. Gary is the CEO of Kennedy Krieger Institute at Hopkins, but he is also the medical adviser for Autism Speaks and has been spending more and more of his time in the last few months in helping to guide this exciting new effort.

Thanks for joining us.

Dr. Gary Goldstein: Thank you, Tom. It's a pleasure to be here.

Richard, I would say the Baltimore Ravens are behind us. And hopefully we'll find support to

join your network as well. I wanted to give you a little background about the origin of Autism Speaks. Before I do that, I wanted to introduce Alison Singer. Maybe she can stand up. I can't see you right now. There.

Alison is the acting Executive Director of Autism Speaks. And she reminded me this morning that Autism Speaks came into being, not 3 months ago but probably 11 weeks ago, to be more precise, and that we have only just begun to think about how we can fit into this roadmap and how we can help support from the private end and private fund-raising the many efforts that are required -- that are ongoing and that are required, to make progress in autism.

I do believe it is an exciting time. I can remember conversations with different funding people about, "Well, why isn't there more money being spent in autism?"

The answer just a couple of years ago was, "Well, money wouldn't make any difference because there just are not enough ideas to pursue right now. There's not enough to do." And something I do

agree with, there probably are not enough people yet in this field, although that is rapidly changing.

I think we all feel different now. I think the advances that we hear about that are so tantalizing from all different aspects tell us that I think resources, more resources, are needed to pursue the leads that are on the table right now and that this field has matured enough and is attracting people from interesting different disciplines that money is limiting. At least that's my feeling.

When I had the opportunity about six months ago to meet Bob and Suzanne Wright, whose grandchild had recently been diagnosed with autism, I came to them with one of our board members at the Kennedy Krieger Institute, Bernie Marcus, to not ask for their support to fund our institutions but, rather, to point out some of the things that you have heard before that Richard has been talking about and which I think is going to be a theme that Tom was alluding to earlier of the need for collaboration, to step beyond individual

institutions and to create an approach, both from a basic science perspective as well as a clinical research perspective of stepping beyond supporting one single program in one city but, rather, to create networks or a network or interacting networks to advance this field. And to do so is going to require more resources, more resources than certainly from the government. And we are hoping to be able to influence that but also to raise more money from the public for this cause.

And I must applaud the successes of both CAN and NAAR over the past decade from start-up organizations. And start-up organizations are important. I think even Microsoft was a start-up not too long ago. These start-up organizations have not only raised considerable money, sponsored lots of new people into this field, but have raised public awareness and have stimulated the government to do what it is doing.

So we met. And I think, in addition to answering questions about the state of autism, the fact that today one percent of all boys, unless I can't do the calculation, Jose, one percent of all

boys in this country have autism, a quarter percent of girls.

This is an enormous problem and may be growing. More work needs to be done and more private money needs to be raised. My main message to them was look how much money is being raised for childhood cancer today, for juvenile diabetes, for cystic fibrosis, for these other entities, all of which need that money, all of which have compelling problems, but each of which is less common than autism. In fact, all of those combined are less common than autism, including muscular dystrophy.

And, yet, the amount of money being privately raised by the public, from the public, for this cause is orders of magnitude less than the amount of money raised for each of those conditions.

And that struck a competitive cord, I believe, in Bob Wright. And I think that was a turning point in saying, "Well, we are going to do it, too," "we" meaning the field of autism and the private sector. What has been the outcome of the efforts in the last 11 weeks? One has been a poll,

a Gallop-like poll, of random people, as can be done at NBC.

Bob Wright, for those who don't know, is the CEO of NBC. And also it's a combined organization, NBC and Universal Studios in Los Angeles. And it's a fully owned subsidiary of General Electric. So it has a lot of clout behind it. They were able, with a volunteer organization, to do a 1,000 telephone call poll and a little bit to discover the general public's awareness of autism, which was moderate.

The interesting last question to me was, "If this phone call was a request for a donation, would you make one right now over the telephone?" And 20 percent of these people, 20 percent of the 1,000 people called, were prepared to write a check for autism.

These are not families. Most of the money today has been coming from families. But imagine if the money for leukemia for St. Jude's was coming from families of children with leukemia. They would have virtually nothing given the incidence of those disorders.

So this was the general public. Twenty percent said they were ready to write a check, even on that phone call. So that gave some push to the feeling that this organization effectively presented to the public could raise much more money and maybe comparable amounts of money as the other disease-focused childhood foundations have achieved.

That is in the fund-raising part. And I did sort of give a little "uh" to that. The question is what would be done with that money and how would it fit into this roadmap. That is what I am just beginning to try to get help from all of you to explore. And I don't have the answer. I know a lot of people are saying, "Well, just what is going to happen?" I'll tell you what has been influencing me and just my background. I'll be quick about this, a couple of minutes or -- two minutes.

One has been travels around this country meeting people. I'm not going to make the list. I have a list here. But I will tell you the people that have been -- I am just more than overwhelmed

by the number of parents who have become not just pushing, not just advocates for this field, but have taken it on and are designing the approach, the most recent of which you just heard, Richard Fade.

This was not done the way I would have thought it would happen, the Autism Treatment Network. This was not six places coming to Richard's and "We know you are a rich guy, and would you give us some money to start our network?" This was just the other way around. And he is not an exception to this. This is his plan. This is a parent plan to say, "We need a network. Who is out there? Who can I get to join this network?" And he is one person like this.

I have now met Denise Resnik in Phoenix, who has got the Southwest Autism Foundation, whatever the acronym is. She is a dynamo. And she is not just out raising money. She has got a plan for clinical research in the greater Phoenix area.

She has linked up and I think was important in getting this company to spin off from the NIH. I can't think of the name of it right now.

Dr. Insel: TGen.

Dr. Goldstein: TGen. It's now in Phoenix. There's not a university there that is very active with it, but they have a big genomic company there. And she is just pushing for this. She is organizing it. Then I meet Portia. I mean, Jon is the outspoken leader here, but you spend an hour or two with Portia Iversen. And here is a mother who is not a scientist. But you won't know that after you spend -- you know, she has read every paper that has been written in this area that is relevant, has her own feelings about which chromosome this is on, and has science to back it up.

I can go down a long list, actually, of people. Jim Simons, a mathematician, lives in New York, chairman of a major department of mathematics at age 29, child with autism. He and a bunch of other mathematicians and physicists started a hedge fund. I have never quite understood what they do. But he has become quite wealthy hedging and is personally identifying incredibly powerful, great scientists who were not

in this field and funding them to do research. He has got an agenda. And he is evaluating the science. He is monitoring what they are doing.

And my point is, I am meeting -- I didn't start out liking this, but I have to admit this is how it is. I don't think there are other fields like this. This is a short example of people -- parents who are not scientists, who are not just activists. Some of them are very quiet. But they're learning the science, and they're directing what is happening. And I think it is something we on the traditional academic end have to really appreciate and understand.

There is a vacuum. I think one reason they are doing this is there is an enormous vacuum. That gets me back to the second minute.

[Laughter]

And that is just what has influenced me in my own background, just very quickly, I direct the Kennedy Krieger Institute. We began with funding from HRSA through a branch called MCH Bureau, which began the university-affiliated programs in 1964 to have sites, now 34 of them around the

country, to train professionals in multiple disciplines to work on the issues of developmental disabilities.

Kennedy Krieger Institute is the first and largest of those programs in the country, ever dwindling in its support, but, nonetheless, we are your largest training program. We train all of these different disciplines. So we are also funded by Administration on Developmental Disabilities for creative community programs. To me, training and bringing more professionals to this field is critical.

And if Autism Speaks can help with that, I am going to -- myself, if I didn't have a Basil O'Connor Award from the March of Dimes, if I didn't have what was then called an RCDA from NINDS, I never would have been in this career.

The idea of having starter career awards, mid-career awards, senior career awards to seduce people into this field is critical. We can push on the federal government to do it, but if we can raise the money in partnership, we can expand the number of people in this field. There's lots more

I can say. I just want to say I know I have met the scientists. I can't tell you how many scientists, Barry Gordon included, are in this field, not because there is money to do research in it but because they have children with autism.

In addition to Barry and our own institution at Hopkins, I am working very closely with Craig Newschaffer, a cancer epidemiologist who switched to autism because of his child with autism; and Paul and Kylie Law, who trained our pediatricians. And they have Masters of Public Health. Paul just completed a bioinformatics fellowship.

He's working with autism. He's the creator of ISAAC, which was initially funded in his work at the Kennedy Krieger Institute by support from CAN. He is now working. We have given him start-up funds to begin working on a Web-based interactive registry, which is just being planned at this point.

My own prejudice -- and it is my own alone -- is that I look at all of the emphasis on genetics and treatment networks that I would like to see also accelerated studies in epidemiology,

particularly with the hope of looking for those exposures, exogenous exposures, that might either provoke or minimize the effect of the genes that might predispose to autism.

And if I see a vacuum in all of the discussions that I have heard so far, it has been an organized prospective and detailed epidemiology studies of this disorder with an eye to exposures that may either limit or trigger those who were vulnerable to autism. That is where we are at. This is, as I say, 11 weeks old. We haven't put together -- we're just in the planning stages of getting advice on how to go about supporting research.

We really, really want to interact with the Autism Treatment Network, with CAN, with NAAR, with the Southwest. People are coming and saying, "Gee, I have this wonderful project. Do you have a few million dollars?" And hopefully it will. We're just a tiny group of people right now. That is where Autism Speaks is at the moment.

Dr. Insel: Great. Thank you very much, Gary. I think I can speak on behalf of everyone here that

there is a lot of excitement about what you and Alison are doing. I think all of us will be eager to work with you and to make sure you are successful.

So in the spirit of collaboration, we are delighted to have you here and hope that this is just the beginning of a much longer conversation as we go forward. Eleven weeks isn't much, but I think there are all kinds of opportunities. Hopefully by the next IAAC meeting there will be even a longer story to tell. So thanks for joining us. We are going to take a break at this point. I would like to get back here as close to 10:30 as possible so we can hear from the Services Subcommittee.

[Whereupon, the foregoing matter went off the record at 10:23 a.m. and went back on the record at 10:34 a.m.]

Dr. Insel: Merle McPherson from HRSA is here to report out more of the details of that, but we have promised her that she will get out by 11:00 o'clock because she has to travel. So the clock is running.

Dr. Merle McPherson: Yes, it is.

Dr. Insel: Merle, I think --

Dr. McPherson: I think I will go ahead if that is okay with you.

Dr. Insel: Go ahead and get started. That's right. And you can start by telling people anybody who isn't at the table isn't going to get any of the money that you are giving out for this.

[Laughter]

Dr. McPherson: As soon as I get it.

Dr. Insel: Please, I want you to notice that Lee is not sitting down yet.

Dr. McPherson: That doesn't count. Well, I apologize for dashing out, but I do have travel that I have to undertake. And I am sorry to miss the rest of the meeting because, obviously, the science that underlies all of this is going to be incredibly helpful as we develop the services roadmap. But our charge was to address the urgent crisis and need for service today based upon the science that exists.

We did meet in November with you and presented from our expert workgroup the roadmap and the

recommendations that they had made. We are back today to talk about a defined implementation plan based on those recommendations.

I have members of the subcommittee here from the federal agencies. They have been a wonderful group. I want to thank them tremendously. Lee has served as the link between the federal agencies and our expert workgroup. And our contractor with Beth Roy, who is here, has just done a tremendous job in supporting us.

So I put up the Services Subcommittee's contributors simply to acknowledge the work that has gone in today. And we have had the official members but also a large number from the various agencies.

One of the things that the subcommittee did was to come together and identify, from the various spheres of services, an expert workgroup. Let me tell you they have done an enormous amount of voluntary work, have been incredibly supportive and helpful, and they are a great group.

Two things we want to reinforce from what we said before is that the expert workgroup and the

map we put together were grounded and imbedded in the President's New Freedom Initiative, which is based on a Supreme Court decision that recognizes that community options must be available for all persons with disabilities.

And as part of that, we were charged with developing community systems of services for children, youth, and families. And we have obviously broadened it to the life span.

The six performance measures, the six programs, the six goals, whatever you want to call them, is strong family-professional partnerships; the issue of early and continuous screenings; the availability of the needed health education, mental health, and social services; and some attention to the complexity and easing at the community level the integration of all the things that we fund so they're much easier for families to use; the issue of youth transition into adult services, work, and independence; and then the issue of adequate financing. That is the six performance measures that underlie all of our work at this point in time.

It is reflected in this diagram -- and that is the other thing that we are embedded in. It is the strongly-held value and belief in this country that persons with autism and persons with disability have full inclusion in all aspects of society.

So this is a diagram that Lu Zeph developed for us that really acknowledges that access to all community services with appropriate accommodation, working, making sure that our disability services and supports are responsive to autism, and then dealing with the access to those autism-specific services that are needed.

On March 22nd, we brought together the expert workgroup and the subcommittee. And the expert workgroup went over their recommendations with the full subcommittee with discussion and comments. And then we spent some time going through those recommendations from the government side and looking at what agencies had some responsibility for the various recommendations that had been given to us.

From that meeting, there came two major

implementation recommendations. There are two major activities that it felt needed to go on. One is to obtain ongoing involvement of high-level federal agency officials to address needed resource support, infrastructure development, coordination, and the policy implications of the services roadmap. We can continue as an interagency group from our agencies, but it does need to go to those higher levels.

And, number two, there was a strong sense that we needed to secure resources for a contract with an entity organization that would convene key public, private, and voluntary stakeholders and advocates in terms of getting broader consensus development on what the service needs are and a strategic plan with very specific actions and milestones to implement that full roadmap.

And I think it reflects our understanding that this is the super highway that is being named, there are a lot of mini-maps that need to be developed, but that we are speaking about a service delivery system that is incredibly complex, is often incomplete, and is made up of

voluntary, private, public resources so that we really do need to engage a very broad constituency, as was pointed out here.

I am going to share with you some of the look that we had off the recommendations and agency sense of involvement with those particular items. But there is a little bit of anxiety by the various agencies as we talked about sharing these because it really represents a snapshot in time that we are going to show you.

Multiple agencies obviously have some level of ongoing activity for most of the recommendations. So you will see the recommendation in a number of the agencies who have resources to put for that, but I want to make it very clear that this is a short-term response limited by our current resources. This is talking about what we can do within the constructs that we now have.

The roadmap recommendations are obviously based upon the six performance measures: achieving family-professional partnerships. And I think the first recommendation gives you some idea of what I mean by that snapshot in time. It is the need to

really ensure ongoing training and technical assistance, both to professionals and families, so that we have a partnership as we move forward in the service area. And you will note that there is significant agency activity there.

There is, at this point in time, a huge constituency that comes from the autism networks of the organizations that serve those, but our agencies also have broad coalitions of families. We support a national organization known as Family Voices. That's in every state. Education supports parent education centers, mental health supports, Federation of Families with Mental Health Issues, all very concerned about autism, all willing to come together so that our ability to build family center care and family-professional partnerships is fairly strong.

You will note that the ones in green are the ones that we have selected out. I am going to talk a little bit more detail about them as we move forward for short-term activities.

The early and continuous development was obviously easy. We could just simply say that we

would support Jose's activities with the screening subcommittee. But we also move forward from the expert workgroup to really acknowledge the need for guidelines, not just in screening but diagnosis referrals, the need for standardization of methodologies, our concern for getting this incorporated into the residency and professional training programs, the discussion of linkages between the primary care providers and that network of community services that is there and somewhat scattered and our interest in looking at how to provide technical assistance and get information out.

Access to all needed services and health, mental health, education, and social services. You will notice that is a huge set of work. And I think one of the messages from the expert workgroup was that perhaps one of the best ways to deal with it was to begin to do some of this practice guidelines, if we could pull together and promulgate the known practice guidelines in each of those fields and develop some of those standards, that that may be a way to help drive

moving the service systems to the various areas. We also talked about getting those in to curriculums and that issue of providing incentives to try to get at this provider-scarcity issue, well-trained providers, more equitable distribution across geographical areas.

I am not going to go through all of these because we are kind of rushing through, but the organization of community-based services for easy use is an incredibly difficult issue in this country at this point in time.

And one of the interesting things that came from the expert workgroup was really a very strong urge to the federal agencies to acknowledge that service development and service integration and services really occurred in this country at the state and community level and that we really needed to support family-driven state and community initiatives to implement creative approaches to the practice and to provide technical assistance to states and communities in those effective delivery models.

Lots of discussion about Web-based and getting

information out and lots of discussions about ensuring that individual plans coordinated across the service sectors. Our money comes out in silos. And I think the big message from the expert workgroup is to work with the state and community level and really try, at least at that family, provider, community level, to get our act together.

The youth transition to adult services work in independence was a difficult one. I think we need to be honest in the discussion that our transition programs are probably weak. And as we begin to talk about extending the life span to ensure adult services, there truly is a gap in that point that we need to address. And we're beginning to look at how to do that.

So a lot of this was discussion about collecting data, trying to start the services early, involve youth in skill-building opportunities and provide an array of services and supports in the community.

The appropriate financing, bottom line, finally becomes dollars. And there some of the

recommendations were really to do some national studies of costs and insurance to look at policies and practices that affect financing, demonstrate the cost-effectiveness of early intervention programs, which we really believe is there, expand the health insurance benefits, and then do some modeling around packages and waivers that we now have.

So those were the recommendations that are in the expert workgroup roadmap that is in your packets. You have that roadmap. And we have been through all of the recommendations. What I am going to do now is walk back with you on those that we selected out for some immediate short-term priorities and some suggestion of what we might do with that.

I think in doing that, we have hit upon some of those issues that government can do something about, that issue of dealing with the comprehensive information that exists in all of our agencies but isn't coordinated and pulled together and the increasing need and the things that have been added here of getting that research

out and translating it down into practice, supporting the screening committee, the professional guidelines, building our technical assistance, just simply beginning to look at the gaps and services for adults, and then deal with the Medicaid.

So improved access to comprehensive information. ARHQ has kindly agreed to take the lead on that. And they will facilitate coordination of all the Web sites that exist between all of our agencies and try to help establish a comprehensive clearinghouse so that the information and knowledge that we now have is better coordinated, put together, and gotten down to children and families.

The Screening Subcommittee obviously is led by CDC. And for this plan -- and I thought it was a very good one from CDC -- to coordinate with the other agencies and partners to increase the current screening, diagnosis, and referral efforts in order to support families and professionals.

There is child find in education. We have a large commitment to early and periodic screening

in our Maternal and Child Health programs. There are screenings done in many of the ACF programs.

And so CDC, in addition to what they are doing, if they will work with the resources that cut across the agencies that we can probably strengthen this is one of the areas that I think all of us feel we can make some very real progress.

Develop and promulgate the professionals' guidelines for service providers. We have agreed to take the lead in that area. We have a proud history of working with the pediatric specialty and subspecialty groups historically in the development of their standards and guidelines.

Actually, we were in the process of convening an expert workgroup of medical providers to address health-related issues specific to ASD using a cooperative agreement that we have with the Weisman Center at the University of Wisconsin. And we have a rep from that center with us. We really wanted to look at a model of health care services from the primary care to the linkages.

I am very excited about the Autism Treatment

Network, and we will be working closely with Jim Perrin on that. We, in truth, just gave Jim Perrin a new grant from our agency, which was to look at evidence base using these six performance measures.

To convene a group to begin working on adults, ADD agreed to take that on. They have a broad DD network of grantees who do provide services to adults and, either through surveys or focus groups or feedback from key informants, we really do need to compile and begin to document better what the services are out there for adults and how to improve and expand them.

Develop strategies for technical assistance to states and communities. We turn to our friends in OSERS. And I have to say all of us have TA capability in our agencies. I think, particularly in the early childhood area, that the TA activities coming from education are a little bit ahead of the curve. And so they agreed to look at mechanisms to link their ASD-specific services with experts on best community-based models and develop some TA strategies and then continue to

work on strategies to coordinate the technical assistance across the agencies on behalf of children and youth with ASD.

I think a strong national well-put-together, coordinated TA service network for all of the states may help us disseminate the good practices that we have. Finally, CMS -- and they're not here today, and they apologize for that, but they have been actively involved with us. They are developing and publishing a monograph "Promising Practices" of waivers that have been approved by CMS, Medicaid for ASD, including detail about how the waivers are structured. That seems to be one of the real world ways that a number of states are attempting to get a better service model for persons with autism.

The next steps -- and before I move to that, I want to acknowledge that in the report that the experts gave us, there are 31 recommendations. We have outlined a way to begin with six of those, but as we work both with our internal coordinating council and hopefully the outside contract, we can begin to take each of those recommendations and

build very much more detailed mini maps.

The next steps for us are that we need your approval of the ASD services roadmap that is sitting in the packets. And we also need your response to what we presented today about the major and short-term recommendations that have come from the group.

We also probably need a discussion with you of a process to obtain ongoing involvement of high-level federal agency officials. And, most importantly, we need to move forward on an implementation plan.

And I would be delighted to respond to any questions or --

Dr. Insel: Okay. Thank you, Merle. We have about five minutes for questions or comments from the Committee. Barry?

Dr. Gordon: Merle, it's tremendous to see this moving ahead. And I think parents everywhere and everybody affected by autism are going to be delighted at getting progress on providing services and understanding how the matrix of services works.

You mentioned several times that this is obviously a federal, if you like, level effort. But much of the effort devoted to autism is at the state and very local level. I just wondered how good your data could be at the federal level to see what is actually going on at the state and local level.

And, second of all, if it's not going to be that good, maybe some of this needs to be preemptive in the sense of almost investigative to find out and have people go into states and communities to find out what actually is being done, as opposed to what may or may not be documented about what is being done.

Dr. McPherson: I agree with you. I don't think we have an enormous database on the systems of care. I mean, that is really what Jim Perrin's new grant with us is for, is to try to look at what the evidence base is generically for children and then look at it for autism.

So that as we respond to those individual recommendations, one of which -- and the expert workgroup was very strong on recommending that we

not do it all at the federal level, that we really support state and community involvement and implementation. So you're right. That's where we need to really know what is going on. That's where we need to comb the data a little bit better. And that is part of what will happen as these get spelled out. There is no doubt about that.

But certainly education helps. I mean, the implementation is at the state level. Now, we have block grants. There are dollars out there. There are programs that we are working. We are into implementation in every state in this country of these six performance measures. So we are at least building on something and with people who know.

Dr. Insel: I think Lee has a comment.

Mr. Grossman: Yes. Barry and I think the rest of the Committee needs to understand the process that we went through in developing this services roadmap. The expert workgroup that was pulled together eventually came up with about 100 bullet points. As a few of you may know, I am a little bit skeptical and critical of anything that is presented as not being far-reaching enough. And

that plan was about as far-reaching as I have ever seen. It was as comprehensive as I think any parent would want to see.

Unfortunately, we can't do all of those 100 bullet points today. What Merle is presenting here is what the federal agencies are willing to commit to at this point in time to move this process forward. And I think that is an extremely important step. It's one that is long overdue and one that we need to get going on.

Your point is well-taken. And the expert workgroup identified that it is truly the field, the local, the county, the state workers that are the ones providing these services and will eventually get to that point. And we in no way ignored those people's responsibilities and certainly their critical aspect of providing these services.

I think that it behooves the Committee here to endorse this. This doesn't mean that the other work, the other I guess 97.3 bullet points, won't be ignored. We are in the process of moving forward on each and every one of those because

each and every one of them is a priority and needs to be addressed.

Dr. Gordon: I didn't mean to imply that I thought you were lacking. If anything, I would like the Committee to write you a blank check so you can do all 100 and the other 100 that inevitably are going to arrive. Yes, give me the special pen.

Dr. Insel: I'm going to assume that's not an action item for the Committee.

[Laughter]

Dr. Insel: There was a comment up here, but you will need to come to a microphone so that we can record your --

Ms. Sullivan: It's delightful to hear that adults are being mentioned. There's a new organization in this country called NARPAA, and I have been given five minutes this afternoon to talk about it. So I certainly won't talk about it here. But it is the National Association of Residential Providers for Adults with Autism.

It is very specific to autism. There are only about 30 of us, less than 30, in the nation. The

president is sitting right here, and we hope to talk later on this afternoon. And we would have some of the data that you were talking about, this gentleman over here, because we're in it every day with adults with autism, serving them comprehensive services in our communities.

We already have standards. We already have some data collected, nothing formal. But we meet, and we are very excited about what we are doing.

Dr. Insel: Thank you. We had heard already that in the realm of services, this is really one of the unmet needs that need a lot more attention. And it is one that we'll look forward to your organization and your comments later as well.

Merle, I know you need to get out the door. And I know you want to have some endorsement from this Committee. I'm concerned that people haven't actually read the material yet. What I would like to recommend is that we do that electronically and that we will have Ann poll the Committee over the next few days when people have had a chance to really dig into this.

The documents which you have sent out which

are the roadmap don't actually have timelines associated with them, so it's not clear when things will get done. And I would imagine that people will want to know that over the next months.

It may be one of the follow-ups for our next meeting. To take those six items that you see as your highest priority and really lay out the milestones that we can look to know how we are doing and that the public can look to know how we are doing as well. But unless there is anything else, I know you had to catch a plane. We are going to let you get out of here.

Dr. McPherson: Yes. I apologize for that. There are significant numbers of the Committee here, and I also have my staff here, who have done so much work: Bonnie Strickland; Monique Fountain; Beth Roy, who is the contractor. And I just tell you that for people who want to ask questions or raise anything, go to any members of the Committee or my staff and feedback for it.

I'm terribly sorry I have to leave today because this is a very valuable meeting for us.

Dr. Insel: Well, thank you for the presentation. We will follow up electronically to give you comments back and hopefully the endorsement to go forward. It is very important for us as well.

Dr. McPherson: Very good. Thank you.

Dr. Insel: We're going to move forward. The next topic for us on the agenda is the database. As you can recall from the matrix goals that we set up, there was a lot of discussion about the need for a bioinformatics resource to really pull together the kind of information that is coming out.

Richard Fade's comments were consistent with that as well when he talked about the need for bringing together information from many different centers into a format that everyone could utilize.

Part of it is that kind of a database. Part of it also is the need to have a way to analyze existing data sets more quickly to facilitate collaborations and ultimately to generate some novel ideas for studying both etiology and treatment of autism.

What we would like you to hear about at this point is a new venture and an opportunity to really take the databases that have been developed to the next level.

We have asked two people from the Center for Information Technology here at NIH to brief us on a project that they have been working on now for several months, Alex Rosenthal and Don Preuss. They're both from, as I mentioned, CIT. The actual office is called the Division of Enterprise and Custom Applications.

I'm not going to take a lot of their time with introductions except to say that these are two people who really understand how to build databases and how to make them as useful as possible in a biomedical context.

So I'm sure, Alex or Don, who wants to lead off.

Mr. Alex Rosenthal: I am going to start.

Dr. Insel: We'll start with Alex, who is the Director of the Division of Enterprise and Custom Applications at the Center for Information Technology here at NIH.

Mr. Rosenthal: Thank you, Tom.

The Center for Information Technology is NIH's Center for Information Technology, obviously, where we provide support for infrastructure applications and computational bioscience.

We first started working with NIMH for the MRI pediatrics project last year. We provided technical support and IT management assistance for their data coordinating center. And then around December of last year, we were asked by Sue Swedo to look into the feasibility of a national autism database.

I mean, it's a big problem, and it's a big project. So one of my first questions to Sue was, "What makes you think that such a large collaborative environment, in fact, may work?"

And the story she actually shared with me is pretty much the same story as what Richard Fade shared with us today. She shared back the story with children of leukemia and how coming up with a collaborative environment really improved their lives. That story really became our inspiration and driver for our future activities.

We immediately recognized that autism is a very special subject for many people who are involved with it and that not only lots of sweat was put into designing solutions that could help. These people also poured their souls and hearts into it. So we paid very careful attention to analyzing existing solutions so that we can use what exists today for the best of the future.

We looked at about six systems that collect various types of data and provide us with some analysis. And we interviewed over 35 people. And we collected and reviewed over 242 documents. I just wanted to explain to you how much of a task this has been for us for the last five months or so.

Don and I are here today to present the results of what we learned and to make a recommendation on how we feel we can move forward with this environment.

I also would like to use this opportunity to give some credit to the rest of the CIT team: Judith Turner, Ralph McGuire, and Shahid Shah. And also we got tremendous help from UCSD folks who

helped us with putting together a nice movie about how we can use NCRR's BIRN initiative to shape up this national autism database.

And with that, I would like to turn this over to Don Preuss, who will work us through the presentation.

Mr. Don Preuss: Thank you very much, Alex. So, as Alex said, we have now been working on this for a few months. Just a quick overview of what we are talking about today, Alex with the introduction; vision and goals talking about the NDAR, National Database for Autism Research; some discussion about organization governance, how this could actually work and be supported; and then some recommendations.

So one of the things in starting out in any of these projects is talking through what are the goals and what are the visions, what is it going to be, and actually what is it not going to be, because there needs to be some border.

So the goal is to establish a national data resource for collaboration in autism research and clinical practice. And a lot of the people you've

heard speaking before me today have talked about those types of things as well. One of the key words we're hearing today is "collaboration," people working together, sharing data, sharing infrastructure to be able to come to resolutions, come to discoveries more quickly.

One of the interesting things is that it also is not any single data type. So it's not any one particular field of study. There are people working in clinical research and behavioral research and neuroimaging and genomics, proteomics. And the field expands and expands. Part of this is also, how do we bring all of that together? So how do we integrate all of this data to provide the support that is needed?

And so the vision for this is to provide for a sharing of research data collected in the process of exploring and testing autism hypotheses, to give the researchers broad access across domains, look to global resources, right? So it's not just sources that are here at the NIH. It may be sources located across the whole world, if necessary, or if found there as well as providing

different analysis tools. There are tools that are available not just in the scientific realm but also in financial, in the intelligence side, that are very good at looking at patterns in data.

And so it's how do we bring those tools and bring them to make them available in autism research and also, critically, how do we set up standards? That's one of the things we have talked about a bit this morning, is how do we establish common standards to allow comparisons across the study.

So this is just a quick graphic with a lot of data on it to talk about this. So what we are talking about here is NDAR. NDAR is not a single box. It's not a computer that is sitting someplace, but it's actually a federated resource. It's data that's located at many sites. It's located in academic institutions. It's located at possibly foundations. But it's located in many places, and it's federating all of this data together to hold together this one comprehensive database.

For the user, for the researcher, they

wouldn't know or see where the data is located. They don't care. They're just looking to do the research. But this infrastructure underlying all of this takes care of that. And so we're looking towards the BIRN infrastructure, which, as Alex had mentioned, is work that has been funded by NCRR, National Center for Research Resources. And it is providing underlying grid, underlying technology to allow all of this to happen.

But as we have been working as well, there are other groups that are working on similar types of activities. So NCI has a project called CaBIG, the Cancer Bioinformatics Grid. And they're looking at doing some of the similar types of activities as we're talking about here: federating data, providing standards.

And what they have been working on much more at the front, at the forefront, has been, how do they create the standards, how do they create the common vocabulary so that all of the researchers are talking about the same thing and as they share data, they all understand the same things.

As you have also heard, Kennedy Krieger have

ISAAC. ISAAC is used in many places. And they have done a lot of very good work in terms of defining all of these different data elements that are used in collecting these assessments.

And the work is standards-driven, but what we're also talking about is by federating in data from autism researchers, researchers may have their own databases. So that may exist at their own site, but it links in to the data.

As you also heard today, ATN is going forward with their clinical work. One of the things that we see, one of the critical issues right at this point, is that there are two groups. ATN and Autism Speaks are starting up with their development of databases. CDC is starting up as well at this point.

If we can come up with some common data standards, if we can come up with common ways to discuss the data, we can actually share all of these together. And what that can provide is for researchers both a breadth of data, possibly from, say, Autism Speaks, which may have a very broad set of data from the parents; the clinical data

from ATN, which provides a depth in a particular area; and then the various research data. But as a researcher starts working on a new study as a new hypothesis, they can start working very quickly on this.

There are also existing database. So there are gene and tissue banks that are in existence. We don't want to copy all of the data related to those, but we're looking to link to that as well as external internet resources. So there are resources such as GenBank, PubMed, PDB, PIR, whole hosts of acronyms that are available that researchers use in their everyday work. They shouldn't have to look at stopping what they're doing, going to query different databases, pulling that data back in.

And, lastly, we have a little R01 researcher here. This doesn't mean that people need to invest a large amount of money into hardware and software. The goal here is that the researcher could sit down with their Web browser and they can start gathering data. The data itself is located somewhere in this infrastructure, but they don't

care. They have gone to a Web site. They have access to their data. They can collect data. They can analyze it. They can review it. They can publish.

So benefits to research. So we have core data set collected with common methods. And that's some of the work that the STAART and CPA centers have been working on and DM-STAT has been working on.

Quicker start-up time. So rather than an investigator having to spend the first three months of their research setting up a database, developing a data schema, finding software, training people, all of this could be available for that researcher in a matter of days. Basically they get a user name and account, have access to the system. They can start working.

Governance, though, is also a prerequisite for the comparison and sharing of the data. So we need to have common standards, groups that get together that agree on how this data is represented, how it is discussed, as well as a resource library for data collection. So, again, in terms of quicker start-up, in terms of standardization, don't

reinvent the wheel each time you start a new study.

If there is work that can be used from other studies, say from a pediatric MRI study, from other autism studies, use those best practices and bring them together. So what this is doing is you heard the word "framework." It's providing a framework for collaboration among the community of autism researchers.

I won't go through all of these, but some of the things it does also do, which you did hear, larger ends, so rather than having to go and gather yet again a whole new set of subjects of children to bring them in to study, we can reuse the data that has been collected on them and start a study much more quickly. It may be that a particular researcher is looking at a slightly different set of data, but perhaps a larger set of data that has been collected can be used already, as well as providing for control cohorts. So as a new study gets started, data that has been collected for other studies can be used for it.

There is a lot of work that is going on right

now funded by the NIH in this area. So, as I mentioned, NCI with CaBIG; BIRN from NCRR; the NCBCs, the BISTI Centers, National Centers for Biomedical Computing; NECTAR; the NIH Roadmap are all funding work in software/hardware data-sharing activities that are very important for this.

So data sharing. So we talked about a lot of the collaboration work, but critical to this is data sharing. We talked about having fair, open, timely, and controlled sharing of the data.

Not all data needs to be shared as a bulk. So there may be some parts of data that are available sooner. Perhaps demographic data can be shared sooner, perhaps some of the core clinical data. Other data perhaps may take a little bit longer, they may need to be validated. Methods need to be reviewed. Possibly somebody has a chance to publish, if that's part of the critical path of it.

There's also some data that may not be made available. There are some things like video, which might be collected but for privacy reasons can't be made available to a very large audience without

some consent. On the other hand, there may be collaborations that can be made available to it.

So what I wanted to do right now was just take a quick moment to show a little demonstration of what we're talking about just to show that some of these things actually exist. This is a demo of a database that is used for Alzheimer's research based on BIRN. The folks out at UCSD were very kind to help us with this. And this is a type of interface that someone might use.

So one would log in to the system. This is just through a regular Web browser for the techie folks. These are all of the systems that are available in the grid of computers. They're located around the country.

One can see what is being used on them. But then one can go into the database, select a subject -- this is a subject that data has already been collected on -- and manage the data for that particular visit. And this type of interface can be changed to be made to look a little bit differently, but it's this type of work that is being done.

One of the critical things about this is that not all of this data is located at one place. This data is actually located at multiple sites. There is data across different types of databases. There is clinical data. There is imaging data.

And so what we are doing here is we are building a quick query across the Mini Mental, age and gender, selecting some additional data from an imaging database, left caudate. And what we are going to do is go ahead and set some values for this query.

Again, this query is running across multiple databases across multiple systems. The end user doesn't know that. They don't care. All they want to know is that this data is linked.

One of the ways that this is linked is by use of oncology, semantic linking between the data. So now we have come back with our results. We'll go ahead and select a particular user, particular subject here, get a quick snapshot of some information about them, and show the details. And what we see for this particular subject are all of the assessments.

And obviously this can all be collected in different ways, reported out by different assessments. There is a whole set of statistical packages that are available with this as well. And what is also important for this is that you don't have to just use the tools that are provided. So one can also in this case -- we're going to look at some imaging data.

Just a brief note, all of this data has to be HIPAA-compliant. So there are audit trails associated with everything. There are access controls for all of the data.

What we will do right now is we are going to just launch out to another application. This application happens to run locally on people's computers. So not all applications have to be inside the system. You can use any application you would like that knows about how to work with this type of data.

So in this case, we're going to be using an application called Slicer developed at Brigham and Women's. And we'll bring up a quick imaging atlas. This is a 3D image atlas, MRI data. And by

highlighting over six different areas, one can see -- moved a little bit too quickly for me. It is actually a mapped atlas of this particular subject image.

We will go ahead and select the region we're looking for. Just click "Navigation." We're going to slide our Slicer up until we get to the area we're interested in. We just need to rotate the image and zoom back in quickly.

And now as we zoom in, what we will be able to do is we are going to start being able to find the particular region. And one of the things that is coming up -- here we have the right -- where are we? We have the right ventricle and hippocampus. And right over there is the right caudate.

And the next step with this is that one can then take that data, link out into other reference databases, link out into other subject data and start comparing -- statistically start comparing the data that is being used.

So what we are looking at with this is taking advantage of technology that exists, taking advantage of technology that other groups are

developing and that have been developed in order to provide this breadth of data analysis.

Just a quick slide for the technical folks in the group. Basically all of this stuff here, the middle stuff, is called middleware or, as the BIRN folks like calling it, is the "underware." It's the stuff that you know needs to be there, but you don't really want to see it. But this is what takes care of the magic of linking all of this data together, the anthologies of the different vocabularies to link the data together.

It takes care of security. It takes care of knowing where the different files are that need to be used in order to actually do all of this as well as bottom distributed computation applications and data sources that are used in this. And this is where, say, an ATN or an AGRE or other groups can be federated into this. And up top, visualization and query mechanisms and data collection mechanisms to be used.

So having talked about the technology, one of the other very important parts is governance or leadership. How is all of this actually going to

work together? So governance is crucial for this to work. There needs to be strong support to deal with the long list of policy issues. And we sat down to work through those. There is a very long list of policy issues that need to get done in order to support coordinating this research, in order to deal with the collaboration, to work with the different protocols and standards.

We have heard a bit about different working groups getting together to discuss certain parts of this. We're now talking about doing it across various different research domains as well as the technology issues and providing for study coordination and logistics and making sure that people are adhering to the protocols.

Even though there are protocols that are out there, researchers will often find something interesting and may decide to, you know, stray from the protocol a little bit. It's just useful to make sure that they are continuing to do it. Part of that is that if data starts being collected not according to protocol, it becomes less useful for the rest of the group to use.

Along with this, though, is also a very important piece, which is change management. None of this is going to be static over time. So as we go across time, whether it is imaging protocols, whether it is assessments, all of those need to be supported taking change. And so the group can decide.

The researcher group can decide how these things are going to change, come to some agreements if there's need for bridges or some other types of support to go from one standard to another, need to be put in place, they need to be put in place.

So we are talking about standardizing protocols, the assessments, metadata. So an important piece of this is metadata. It's not just the data you collected. It's not the yes or no answer. While that is important, it is also important to know how it was collected, who collected it, when was it collected, was it collected by someone who was certified to collect this data so that you as another researcher or someone looking at the data have some comfort

knowing that it was collected sufficiently well that you can use it with your data as well as if it were collected by you as well as we are talking about common data elements and training.

Training we have heard some other folks discuss as well. It is very important to make sure that these are all being done the same way, that people know how to actually use the various tools, assessments, and protocols. But, as I mentioned before, there needs to be an exception process. Not everything that can be standardized should be. There are a lot of areas in research where it is not yet ready. There are always new cutting-edge areas.

People are working. They are thinking about using research in a slightly different way. So we need to understand that there is an exception process but also support nonstandard data collection. Even though we can't possibly standardize on some of these things, it could be very useful to collect it. It may be useful for another researcher to look at the data.

So just a quick governance slide structure,

fairly common I think to most folks, looking at org charts but having a steering committee on top, both a scientific workgroup and a technical workgroup. And then for each of the different data areas, different research areas, clinical, neuroimaging, genomics, different working groups to help work on the standards for those groups.

And along the back here, though, each of these groups also needs to do all of these other areas. There's the protocol; support and design; creating standard measures; instruments; creating the common data elements for use; any application development or integration that is needed; and, lastly, operations.

You know, if this is going to work, there need to people, a help desk to call if you have questions. There need to be people supporting this and, as I mentioned earlier, change management along the side here supporting all of these things. There is a quick set of some policy subcommittees that we have thought of, some policy committees dealing with IRBs, whether they are common IRBs, whether IRBs are distributed and

common language used dealing with the question of non-NIH linkages.

So how does that work? What are the issues that come up with that data sharing and access control? How soon is data shared? Who gets access to what data, if there are some questions about that, and dealing with some of the intellectual property, copyright publication issues. It's an issue the group needs to discuss and come up with some policies in it.

To support this, on the left inside is we recommend a consortium office to support NDAR. These are the people to help just to make sure that all of this moves along, coordination, logistics, some project management, also to act as the place where all of the standards get focused to some reference implementations. Other people could develop applications of their own to work with NDAR, but people shouldn't have to develop their own applications.

We are dedicated to using open source, open development, open access, as well as, very importantly, data federation. That doesn't mean to

say that if there are applications that are out there that are commercially available and work very well, that they shouldn't be used, but that we are very strongly looking towards open source to allow the community itself to assist in the development of all of these.

So, as I had mentioned, some of our recommendations govern these workgroups, putting the library of protocols and standards, very critical, collaboration with the other programs that are out there: CaBIG, Autism Speaks, ATN, CAN, BIRN, ISAAC. A lot of people are out there doing similar work. We need to work together. We need to collaborate on these, talk about federating with the other projects, those that are starting up now.

And, very importantly, as I mentioned at the beginning, there are a lot of people that are working in this area right now from NCI, from all of these other areas. We need to just use their work. That will help accelerate the development.

So one of the questions is, "Well, when does it all happen?" talking about a phased approach

for this in terms of getting governance group in place very soon, portal the subject tracking. There are some core areas that need to be provided for anything to occur.

So the subject tracking way to capture data for clinical and imaging data, coordination with the community, as mentioned earlier, incorporating the pediatric MRI protocols, looking towards model-driven development, rather than people sitting down and coding word by word but looking at higher-level models -- this is something that the ISAAC program is looking towards right now. Then next year working on getting the contents of these things filled out, protocol library, protocol mapping, so that one can actually create a structured flow of all of the studies and reuse different pieces of it, begin working with the analysis tools. Anonymization is a critical piece of this as well.

So this needs to be done so that it is not a highly labor-intensive activity, which it currently is very often. To make data public, one needs to put a lot of work into the anonymization.

And then going forward, 2007 is extending operations to support other groups. But to start, it is really to support a single study at a few different sites in these activities, a phenotype/genotype-type study.

And then as we go out further through the out years, I am sure all of this will change, develop into some final quick thoughts. If we wait for the moment when everything is ready, we shall never begin. Just we have got to get started. I think this is a critical time, just from everything I have been hearing.

The second quote came up in one of our discussions. One of the questions we had had was, "Well, could we really talk about having standards and having all of the researchers agree to it?" We got the answer of yes. So Einstein over here has been our running logo through the project.

And, lastly, Michael Leavitt just released his 5,000-day plan. This is just a quick quote from Michael Leavitt, Secretary of HHS: "Play forward in sports and work. Gain an inch by a forward lean, an absolute commitment to be purposeful in

our next steps to get our job done by doing, not simply reacting."

Everything I hear from this group -- and that was one of the very encouraging things as we have been working with the office and community is thoughts how everybody is looking at this. It is really, how do we go to the next step? How do we make that correct next step, as opposed to doing all sorts of different things? And that is from everyone, the researchers, the parents, the advocacy groups, all of the different spokes we spoke with. So it has been very encouraging.

I don't know if, Sue, did you have some follow-up comments you wanted to make or should I open it to questions?

Dr. Swedo: Well, if you take that slide off, maybe I could make a couple of comments. I just want to thank the consulting group. I think that CIT really did an incredible job. When I was here last meeting, I promised that we would have an answer for you. And they delivered for us. I am absolutely excited.

I know the model of leukemia has come up so

many times that people are getting a bit tired of it. So I just wanted to share with you my perspective on it. And that was that I was in pediatrics residency training in the late '70s or early '80s. And when I started, 95 percent of our patients with leukemia died. By the time I left Northwestern 6 years later, 95 percent lived and lived with a cure of their disease.

So that's the kind of timetable we are trying to set for autism. And I think that without this national autism database, we can't get that done. So that's pretty much what I would have to say.

Dr. Insel: Thank you, Sue. This is an example where sometimes it is an advantage to come late to the party because a lot of the technology has already been developed. We can piggyback on what has already been going on in BIRN and CaBIG and some of the other efforts.

Obviously from what you have just heard and what we were talking about earlier in the morning, there is a cultural change that is still required. And that may be a much more difficult part than changing the software and hardware because this is

a different way of doing science. And it is going to require a change in the practices of many of our researchers.

We are hoping that Jon Shestack, who has been very interested in this area and actually raised this question for us at two previous meetings, would serve as a discussant on this and give us some feedback of where this effort is going.

Mr. Shestack: Okay. Well, I have to say it's sort of like I feel a little bit like someone who has been asking somebody to marry them for five years and finally hear those magic words, "Oh, all right."

[Laughter]

Mr. Shestack: So you're very happy, but you can't forget the fact that you have been asking for it for five years.

Dr. Insel: Jon, think of the anticipation.

[Laughter]

Mr. Shestack: It's true. So I think, you know, from the first presentation of this, this is fantastic. And it is visionary. And it does build on things that many people have been talking about

for a long time and people have been doing in various parts of the world. And hopefully this will bring them together.

It's also important to know, I think, why -- have some historical perspective and know that up until now, data management, a common data platform, and the lack of it has been a tremendous, tremendous problem in autism -- I can only speak about autism, I can't speak about any other disorder, but to the point that it was really kind of hampering progress and sort of scandalous.

Particularly now when we have no money, there is no new money going into autism, this is more important than ever because this makes everyone's money go much, much further.

So one of the things I'd like to ask about this maybe you can tell us is what kind of financial resources will go to this. What is the timeline? The other thing is, Tom, you mentioned that it will require a little bit of a change in the way people think. That may be true. There may be individual investigators who haven't yet come

up with standards across sites that really have to now in order to take advantage of this.

So I want to say, one, at least from Cure Autism Now, but I'm sure it will be also from NAAR, you would have full support from us in trying to make this new system be the system that everybody uses, although we spent time and money on ISAAC.

If ISAAC could be part of it, great. If it isn't, it's the idea behind it that is what is important. So what are the positive and negative incentives that NIH will put in place to make sure that this is universally adopted and fast? Time line investment.

And then, although we do dispute the amount of money that NIH claims they spend on autism, if, in fact, there has been like an average of $75 million spent over the past 4 or 5 years, there must be a lot of data out. Is there a plan to try and get historical data into this system? And have we included everybody? Will this be something that will serve CPEA sites, STAART sites, the new CDC stuff, and any individual researcher with an R01

who wants to listen?

Although there are people who don't like the idea of data-mining and dredging, if you come up with something good by it, it's a great idea. So we'll just support the individual investigator who wants to do that. So those are some of the -- the final question is, what about imaging, which seems to be the next -- you know, there is some brain banking. There is gene banking. There is an NIMH repository and data repository.

But imaging seems to be the next big thing. Tom mentioned the normative. That thing you were talking about was only normative children's brain analysts, right? So no autism images yet collected that follow standards, I mean, where everybody is working on consistent standards, is that right? And this will hopefully address that. That is the list of question.

Dr. Swedo: All right. I'll start backwards, and we will work our way up. The imaging standards are being set. Institutions are already starting to work together. In fact, the STAART Neuroimaging Committee, the CPEA Neuroimaging Committee met

together at IMFAR and are working very hard to make sure that they have common protocols to the extent possible.

The very exciting thing about this -- and maybe Alex or Don can speak to this more -- is that it allows analysis of data without necessarily having to have the same degree of commonality. You get it down to a raw data point that allows comparison. And that addresses your question about historical data.

I think one of the issues as I came again late into the field was looking at the amount of time and energy that had been spent to try to rescue data that had been collected in years past. I think there are some data that are absolutely amenable to that. And it's appropriate and reasonable to do that. There are other data in which the cost of standardizing it is greater than the cost of collecting it new. So we just have to look at it from that perspective and consider at all times a cost-benefit ratio.

The question of inclusivity, maybe, Alex, you would want to speak to this, but that was the

goal, to have this be something that a graduate student, a summer student, would be able to think of a question, go through the training for access to the system, and get in there and mine this data for everything it is worth.

The question about access has got to be balanced against the issues of privacy and the HIPAA requirements, but that is actually the job of the database. They're the ones that need to set up the firewalls and the protections in such a way as they talked about, the presentation talked about, the tiered access. Some things will never be open to more than a very selected group of individuals. And others will be fairly quickly opened to the public.

I think your final question was about cost. For that, actually, Alex, can you --

Mr. Shestack: Incentives.

Dr. Swedo: Incentives. Oh, I can speak to the incentives first. So the incentives -- my colleagues are here with me from the NIH. We have spent many, many weeks talking about incentives and how to be.

I don't like the carrot and stick analogy. I don't think that is appropriate here. What you do is you incentivize by making it of benefit to every individual researcher. The ones who have the greatest cost in participating are those that are contributing their data and opening it up to the public relatively quickly in the process.

So that can be incentivized through a new standard of operation. And the NIH is actually taking the lead on that. They now require public sharing of all publications. And data-sharing policies are in place for many of the institutes as they give out the money.

Mr. Shestack: But will you consider giving supplements? I mean, this will require a lot of work for some people to do this but work that they could do with the supplement.

Dr. Insel: The way we've handled -- because Genome has some of the same issues, as you know, Jon. And there we have a very clear data-sharing policy. In that case, we ended up doing that to try to incentivize.

I suspect this will have the greatest effect

going forward because I think that a lot of what we want in here hasn't yet been collected or hasn't been collected in a way that will be of great value, both with imaging but in other areas as well. So I guess I am less concerned about how we incentivize those who have done their work five, ten years ago.

Mr. Shestack: And the timeline for getting started -- that's the timeline. So, Sue, will be using funding that was set aside in the STAART budget, which was like $500,000 a year for data management? Is that --

Dr. Swedo: Well --

Mr. Shestack: I'm starting to get like really specific, but it's really an important project.

Dr. Swedo: Yes.

Mr. Shestack: And everybody in the Office of Research can benefit from it. So it's important to really get the details from it.

Dr. Swedo: And I think that all of the institute directors as they heard the presentation were unanimous in their agreement. I don't think that the $500,000 that was set aside will be

enough. And we need to find new money.

Mr. Rosenthal: Yes, that's right. We spent a lot of time looking into staffing for this and budget. And we came up with a few options. But $500,000 is not going to be enough. It's a huge project. I mean, if you compare this -- if you want to compare this with another project at NIH, the proper project probably to compare it with would be CaBIG, which is, you know, a huge contract and a large internal operation.

And, on one hand, the volume of what we are doing is much larger. But, on the other hand, the scope of what we are trying to achieve is very similar. We are going pretty much for every domain of scientific information, trying to come up with standards and improve collection -- proactive data collections.

Our vision is to come up with a number of standard subjects. So we can't come up with a single standard. Science is not done that way. But hopefully we can come up with a number of standards and then come up with a way to interface with small scope standards on the fly for

something like BIRN, for example, where even if data is collected in many different agreed-upon ways, this graduate student from Iowa can then get online, and just using his PC can get on that infrastructure and without spending any money on recruiting his own subjects and asking his own questions, you know, be able to analyze what already exists. Basically in this digital world of information, that's our vision.

Dr. Insel: We have some wonderful examples where this is already happening in genomics where genes have been identified from graduate students, sometimes not in Iowa but in Bangalore or in far-flung places, who simply have access to data. Increasingly, as we often say around here, biology is becoming an information science. And so it is access to information that is often the rate-limiting step to being able to make discoveries. It should happen here as well.

Jim?

Dr. Battey: Is it anticipated that there will be a standardized, controlled vocabulary used for this database in the fields? Because without that,

it is going to be very difficult to integrate input from the diverse variety of sources that you have outlined here.

Mr. Rosenthal: In fact, the answer is definitely yes. And you can go ask for a complete end-to-end analytical ontology, which, as you know, Dr. Battey, is very difficult to build, or what ISAAC did. They came up with their own standard definition of terms compliant with things like HL7. And you can do it that way. But we certainly believe that the only way to come up with over-arching standards is to actually have a control dictionary in place.

Dr. Battey: And presumably the database will reject any entry that is not part of the dictionary?

Mr. Rosenthal: Yes.

Dr. Insel: Jon?

Mr. Shestack: So this will be administered? This will not be done as a contract with a private company? This will be administered ultimately by a division of the NIH?

Dr. Insel: The way it is going forward at this

point is this would be under the domain of CIT, which is the information technology part of NIH.

Mr. Rosenthal: The way we're envisioning this at CIT, we are not going to build everything from scratch, obviously. There is a lot of good work out there, and we would like to reuse that. So there will be some activities happening in academia and other entities that have already developed software that we're going to adapt.

As Don showed in one of his slides, we were proposing the Office for Autism Research at NIH that will provide overall leadership, scientific leadership. We believe that scientific leadership is critical. CIT can provide information technology expertise and infrastructure, but the scientific leadership is absolutely critical, just like in business applications, you know, business domain expertise is absolutely critical.

So it's definitely going to be a joint project, and we will do our best on the technology side working with you guys.

Dr. Insel: One of the things, though, that we have been hearing all morning and I think will be

critical here as well is to make this a partnership where you have got often the information coming in through the advocacy community. I mean, you heard from Gary Goldstein and from Richard Fade earlier about these spectacular efforts to bring a lot of data to one place and to try to make sense of what is now a pretty chaotic set of sources of information.

So what we need to think about is how all of this can be integrated and be done in a way that serves everybody. So even if it lives here at NIH, that is simply a host. It is not meant to be in any way a barrier.

Mr. Shestack: No. My comment actually was that its host was a nonprofit or an academic institution with some stability and longevity that the community knows has a charter from Congress to be around for as long as it needs to be around.

I also just wanted to reiterate what an incredible opportunity it is to do this now. What we had before is important, but what is going forward to get ATN data using whatever the basic platform is, to get phenome project data as that

is starting. As STAART centers get renewed and those projects get expanded, it is an incredible opportunity.

I would just like to ask -- the repository we know about most is AGRE and then the NIMH genetic repository, which works in only one sphere but seems to be working pretty well. Does anybody know? How would that coordinate with this effort?

Dr. Swedo: That would be a piece very similar to the neuroimaging piece. So the BIRN network was set up to handle neuroimaging data. It was then expanded to do multi-disciplinary projects for schizophrenia was one of their first tests.

And we see the genome being folded in just the same way here. And that was actually one of the easier ones because of the hard work that has been done on working with diverse groups to pull all of the data together. And it has a standardized format already.

Dr. Insel: That's one of the primary cores that feed in here. In fact, that is probably the best model we have for doing this. That has also been very successful. It is part of the

inspiration for moving this forward, the easiest kind of data.

Barry?

Dr. Gordon: I think it's a fabulous effort. And some people around the table know it is something I have endorsed before as well. And one of the things I really appreciate is you're putting in nonstandard data.

I want to make sure that that is not misinterpreted because when we hear the data dictionary or anything that doesn't conform to the data dictionary, because although Einstein did wear pants and shirts, that's not what he became famous for.

In fact, I have heard that his pants and shirts were not considered really, you know -- and, if anything, Einstein's thoughts are what we think he was famous for, not his sartorial choices. And most people didn't understand his thoughts at the time they were proposed.

So that there would need to be a place where Einsteinian-like thoughts could be in here, even though no one might understand them.

The reason I also bring that up is because of the representatives around the table and in the room of private groups, who are particularly interested in pushing perhaps frontier-type work, which, by definition, is going to run ahead of any standards committee if it's done right.

So I know you have thought about that. I would like that whole big block devoted to that. But I just want to make a point of emphasis.

Mr. Preuss: Yes. That actually came up with some of the discussions with researchers who were saying the exact same thing. They were saying, "Look, you know, there are things that we're doing right now that probably no one else is interested in. And we probably don't want them to know that we're interested in it if it doesn't work. But, you know, at some point in time, other people may be interested in it and they do want to store it. And they may want to make it available long-term for other people to use."

Mr. Rosenthal: What you are pointing out is one of the biggest differences between a research system and a business system. So we are not going

to make you comply with our existing standards for any data you want to put in.

So some of the data on this grid will be unstructured free data, but at some point we'll try to make it structured. So periodically it will come back and see if it makes sense to make it structured.

So at this point, it is pure research. And if you don't know where it is going, maybe six months from now, you will have a better idea. And at this point, maybe there is a need for a standard around it. Yes. We are not going to come up with a rigorous, non-penetratable environment for you.

Dr. Insel: That's a great point. And it's one of the things that remind us that, even though this appears to be a sort of a top-down approach to science, it actually will never succeed that way unless there is an opportunity for all kinds of unexpected findings to be incorporated.

Richard? And then we're going to move on after that.

Mr. Fade: Actually, I just wanted to reinforce something that Jon said that I think is really

critical for this thing to move ahead.

First of all, you have done a great job with a very complex topic. And I congratulate you on your vision in this area. You know, the technical side of this, though not simple, I think is attackable in the ways that you described.

The thing that I see as very daunting are what I will call standards for data collection and protocols, establishing those, and what I will call standards related to collaboration. And those are very well sort of captured in the prior presentation.

And so this notion that Jon was asking about, you know, in what body do you institute the management of those things, you know, the Department for Autism Research or whatever you wanted to call it within the NIH, I think it is going to be critical to establish that and, as Jon mentioned, provide for its continuity, you know, and ongoing governance because it is going to take something like that to effectively work with all of us.

I mean, we are sort of the twinkle in our eye

the data that we are going to create; whereas, you look at an organization like CAN with AGRE they have created and NIH already have large databases that exist. But you are going to need that office to really deal with those two issues, which I think, frankly, they are about people, they are about IRB, they are about sharing, credit, all kinds of very thorny, complicated things.

And, you know, their work is pretty straightforward on the IT side, frankly, even though it's complicated. But I would really encourage you heartily to establish such a group and give it funding. And your half a million dollars I think might be adequate for the scoping of this project.

You know, you might get a really good scoping and timeline of this project. And then, you know, these guys are smiling, but I think that is the reality of the situation, but it is so worthwhile. And it would make our efforts so much more effective if you could provide some leadership in this area.

Thank you.

Dr. Insel: Great. Last comment?

Dr. Lajonchere: I'll be brief. As the Director of the AGRE program and a huge investor in ISAAC, I can't tell you how thrilled I am. And if there were an "American Idol" for data technology award, you would get it.

[Laughter]

Two quick questions. Number one, one thing that I see as a deficit in our field is a normal control population. And I wonder whether there would be any efforts to include a normal control population as part of this endeavor.

And the second question that I had was how much money is the department willing to invest or is the government willing to invest to start working now to further develop things like ISAAC, things that many different people have already gotten the ball rolling.

I guess what I would like to see is a timeline in terms of what things -- if you had to triage all of the things that you need to do, what kind of resources or plans are available to start with things that are already going?

Mr. Preuss: Okay. I probably don't have enough time to do all of that, so perhaps we could talk a little bit afterwards.

In terms of the controls, there is the pediatric MRI study that is going on. That data is going to be made available. We have had a couple of people talk about that. And that is going to provide a wide range of data, both imaging as well as behavioral and clinical data.

And that's been a longitudinal study going on for six years. So that is going to have a wide range of data from 4 weeks of age up to 18.6. And somebody can correct me if I am wrong on that one.

In terms of priorities, that was what is on the time line. I think, as Richard had said, one of the critical pieces, though, especially because there are these three other activities that are getting going, including probably one you will hear from the CDC this afternoon, the CADRE activity, is to get the governance to get the common standards, common data elements in place so that, even if all of the software and technology isn't in place, we will have a common vocabulary.

We will be able to work as we go along further.

And so that, I think, is one of the key pieces to get going. There are obviously very important pieces to get done with developing additional software to support a full study, including the subject tracking, including data collection in each of these areas. But I think, as Richard said, I think governance in the standards is very important up front.

Dr. Insel: Okay. Thank you very much. I am concerned about the time given that we have one more presentation before lunch. A number of people have asked in the past that we spend more time talking about environmental influences in autism. So we have asked Cindy Lawler from the National Institute of Environmental Health Sciences to give us a progress report on where we are in looking at provocative clues and/or false leads.

Dr. Lawler: Thank you. I think most of you are aware that the National Institute of Environmental Health Sciences is still a relatively new player in this field, although, thanks to Autism Treatment Network and Autism Speaks, I guess we

are no longer the newest kids on the blocks. But we're still fairly new.

We became a member of the NIH Autism Coordinating Committee about five years ago. I would like to share with you today my perspective of the path of progress in this area over the past five years.

These are the questions I will touch on, questions anyone new to this field would have. Is there room for non-genetic influences in autism? You know, what is behind all of this increased interest? Is there good evidence for environmental influences? How do you even study this? Are there any tools or resources that are being developed? And, most importantly, how much progress has been made?

If I had to show just one slide of progress, this would be it because I think that while the scientific field is still heavily weighted towards genetic explanations of autism, there has been some important movement in the scientific community towards acknowledging and considering that there may be environmental influences that

play a role. And this is a very important sign of progress.

The reasons behind the bias toward genetic explanations, I think we're all familiar with the kinds of genetic information that is available, the strong data from twin and family studies indicating a high degree of heritability.

We know that autism is associated with some other known genetic disorders, such as Fragile X. And we have seen a lot of gene association studies coming out. Even some of them have been replicated.

So in the face of that very strong evidence for a genetic basis, why are we considering environmental factors? If we look over the past five years, genetics is still a major driver in the field of autism. And new and exciting findings are emerging.

In contrast, the studies to look at potential environmental influences are much less well-developed. However, I would like to point out that those studies can and do draw from a much larger field of children's environmental health, which is

a mature field and has data coming out that provides strong biological plausibility for considering environmental influences.

So we now know much more about low-dose effects, critical time periods of exposure, sources of susceptibility, and how genes interact with the environment to produce dysfunction. So from that perspective, now is the right time to look at the environment and autism.

It is probably useful to touch on some of the initial public concerns that raised attention to environmental influences. You should all be familiar with this figure or one very much like it showing the dramatic increase in the number of autism cases. This is from California data in the last decade relative to some other developmental disabilities.

There are other ways you can look for this type of trend. This is data that was published more recently comparing autism rate in cohorts that were formed from birth year.

So the increase in rate you see with a vertical separation of these curves and, again, a

large increase in prevalence. When you analyze the data in this manner, it's not shown on this slide, but if you look at prevalence of speech and language impairment and mental retardation, you don't see these kinds of time trends.

So what do we know? We know that the rate is clearly going up. And we know that this increase is very widespread geographically and demographically. We know that there have been administrative and diagnostic changes over this time period that can account for some of this increase. And what we don't know is how much of that increase can be attributed to diagnostic and administrative factors.

There really is no way to go backwards in time to answer this question and figure it out, which means we don't know what the true increase would look like. If we could go back -- and we don't yet know what exposure factors might have been contributing to that increase.

A second major public concern that has received a lot of attention was the idea that the increased rate was related to vaccinations, either

MMR or thimerosal administration, the ethyl mercury present as a preservative.

I am sure that you are aware that the Institute of Medicine conducted a thorough review of many existing studies that bear on this issue and came out with their final report in May of last year rejecting the idea of a link between thimerosal and autism.

Now, I am aware that there is not universal acceptance of that report and that some public concerns do remain, but I think what we do know is that some very methodologically rigorous epidemiologic studies taken together do not support the idea that vaccine exposures contributed to this very large increase in autism rates that we saw over the last decade.

What we don't know, you know, we don't yet know whether the relationship between total mercury exposures in autism and we don't know whether some small percentage of children are susceptible to some toxicant that has increased in levels over the past decade. And we don't know whether that increase might be associated with

autism.

We do know that an environmental exposure can dramatically increase autism risk. And the best example of this remains the work here. Patty Rodier and her colleagues have been pursuing this for some time.

Children born to mothers who had thalidomide exposure during early gestation had very dramatically increased rates of autism. And by using the known relationship between the period of thalidomide exposure and some of the physical structural abnormalities that are observed, they were able to note that the children exposed to thalidomide who developed autism had some very subtle dysmorphologies that suggested the exposure was between embryonic day 20 and day 25.

Now, no one is suggesting that thalidomide contributes to cases of autism today, but these data are essential. They do provide proof of principle. You can have an exposure in early development that dramatically increases autism risk.

Patty Rodier and her colleagues have actively

pursued this lead. And it has been very fruitful. Her studies are funded, I think, both through the CPEA and the STAART centers.

So if we can't identify some other compound, like thalidomide, that just had a blatant dramatic effect and we accept the idea that autism does have a strong genetic component, then the reasonable approach to pursue has been looking at how environmental exposures exert effects through their interaction with autism susceptibility genes. So the best sorts of studies are ones that can really detect gene-environment interactions, rather than examining these two factors separately.

This is the very simplest example of a kind of study that could be done addressing this. In the same population, you measure genotype exposure and disease. The genes you would look at would be ones you might suspect would be influenced by the exposure or would put the individual at risk of the disease. For instance, you may look at a metabolism gene that metabolizes pesticides and by metabolizing them detoxifies them.

Individuals with one variation of this gene may be protected from pesticide exposures; whereas, you know, another genotype may be at risk. The important point here is that you are only going to be able to detect that association if you have got within your group high exposure to pesticides that you can measure and that genotype, that at-risk genotype, is represented frequently enough in your population. You need both.

This is the kind of paradigm that is applied regularly in children's environmental health developmental studies. And I have just provided you with an example of this that was published last year. This was a study conducted in New York.

About 400 women were enrolled in early pregnancy. They were known to reside in areas where there was significant pesticide exposure. Pesticide exposures were measured during pregnancy. Genotype of the mother for a pesticide metabolism gene was identified and for the child as well. And then a number of measures of fetal growth of the newborn were taken.

Importantly, if you looked only at pesticide

exposure, you stratified according to pesticide exposure, pesticide exposure alone didn't predict anything about fetal growth. The same thing, if you only looked at genetic variation, you only looked at the poor metabolizers, there was no association.

But if you looked at both, this genetically determined metabolic activity of the mother and the pesticide exposure together, so you were able to sort on both variables, you knew not only who the poor metabolizers were but who had the highest exposures, they were able to identify a relationship, a gene-environment interaction that predicted something about fetal growth.

This is another example of the kind of study that is being conducted. This was published last year by Mady Hornig and her colleagues at Columbia University. She indirectly looked at gene-environment interactions by choosing three mouse strains that were known to have different responses to mercury-induced autoimmunity. And there was some evidence that this difference in susceptibility was linked to genetics.

She measured the effects of thimerosal, the ethyl mercury-containing compound, on behavior and brain morphology in these three mouse strains. What she found is that the effects of ethyl mercury with the dosing paradigm that she used were observed only in the autoimmune- sensitive strain. Now, these were very proactive findings.

The NIEHS is supporting direct replication of this study. Assuming that it is reproducible, then important questions that remain, you know, what is the genetic basis of this effect? And, more importantly, how do you translate this to public health? Are those genes involved in children with autism or other kind of developmental disorders?

I want to tell you a little bit about some of the key resources that are under development that are going to help answer some of those kinds of questions. These include the Environmental Genome Project and the Center for Rodent Genetics. Both of these are NIEHS initiatives.

You should also be aware there are a number of population-based studies that have been initiated. They are looking at risk factors, including ones

funded by the NIH and ones by the CDC. Animal models are being developed and STAART and the CPEA networks and our environmental health science networks as well that will be critical for dissecting gene-environment interactions.

The first resource, the Environmental Genome Project, was launched several years ago by the NIEHS. And one of the major activities has been to re-sequence DNA from a representative sample of individuals to identify common polymorphisms in what are called environmental response genes.

So these are the genes that were selected because they were likely to be targets of toxicants or somehow be involved in the cellular response to toxicant exposure, include genes involved in DNA repair, cell cycle control, et cetera. And as these genes are being re-sequenced, that information is placed in a publicly available database so that researchers can go to that database and identify polymorphisms that may be fruitful to pursue in the context of their epidemiology or clinical studies.

The second initiative was launched more

recently, last year at our institute, the Center for Rodent Genetics. And the first major activity in this initiative has been to issue a two-year contract to Perlegen to completely sequence 15 commonly used mouse strains.

And, again, the data are being made publicly available as the sequencing proceeds. And this will provide a great resource to try to identify the genetic basis of phenotypic differences that are often observed between strains of mice. So we expect that to be an extremely useful resource.

So some studies are in place. Some key resources are being developed. But I am still not happy. It is not enough. And I'll have to come back to the most salient fact: still, not enough research is being done within the mainstream autism community to examine environmental influences.

So they haven't bought in as much as I would like them to. Why? This is the top six list. We're still battling the idea that autism is primarily genetic. And the leads -- some of the leads that are coming out for environmental influences are

very provocative, but they are not necessarily compelling in many cases because of the methodologic limitations of the studies that produce these leads and the lack of well-characterized populations to really confirm and extend those leads.

I've mentioned some of the difficulties inherent in studying gene-environment interactions. But, you know, there are some bright spots as well. Movement is occurring more slowly than I'd like. You're beginning to see it in the published literature and at scientific conferences as well.

This is an example of a paper that was published a month or so ago that laid out very nicely a strategic plan for looking at gene-environment interactions in autism and for each of these steps identified key considerations for selecting environmental agents as candidates and candidate susceptibility genes and issues about replication. So I think this is a great example of how we are beginning to get attention and attract more scientists.

There's lots more evidence of progress. Most important, I mentioned earlier we can't go backward in time and ever figure out what the true increase was, but what we can do is if we have these reliable surveillance systems available, which CDC has initiated, now has a network, we can be in a much better position to interpret any future changes in autism rate.

So looking forward, things are looking good. As I mentioned, there have been several population-based studies that have begun or are well underway that are examining the potential role of environmental factors in autism.

So these are the kinds of studies that have population-based controls that have a significant number of individuals that have well-characterized cases to be able to, in the broadest way, examine a range of exposures and provide very strong leads to the research community.

I hope that the presentation after lunch by Isaac, he will give you an example of some of the exciting findings that are coming out of his center. Many new tools and resources are being

developed, biomarkers, some of the gene sequencing efforts to support gene-environment interaction studies in animal models.

And together, I think, on balance, the news is good. Progress has been made. It's slower than I would like, but I think it has been real progress.

I will be happy to take any questions or comments.

Dr. Insel: Thank you, Cindy.

We have about ten minutes for discussion. Questions? Comments? Lee?

Mr. Grossman: Cindy, thank you for presenting to us because, even though you may have presented kind of a pessimistic viewpoint of the number of people that are in this field, the ones that you have chosen in New Jersey and at the M.I.N.D. Institute are amazing.

I've been studying, looking at the work that they're doing. And I find that they're perhaps light years ahead of perhaps any other institute in terms of coming to some significant results over the next few years. And NIEHS and your two grant recipients really need to be congratulated

on the efforts.

With that said, and then going back to your point, are there any plans for NIEHS to expand these centers that you have, the current centers, or to add more?

Dr. Lawler: I think we are considering a range of possibilities in the context of the merged CPEA and STAART networks. We're considering the next re-competition of our children's centers and what components we will like, what kinds of research we will encourage.

There are other specific projects at mental health, like this Autism Phenome Project that -- I have had some discussions with Sue Swedo, and I think Isaac Pessah has as well. That would be a great opportunity to add on some environmental exposure information and then store some biological samples for future hypothesis testing.

So all of these options are in play right now. We have a new director on board beginning next week. Next Monday, the 23rd, will be his first day. And I will be having some substantive discussions with him about these very numerous

possibilities.

Dr. Insel: Yes, Lu?

Dr. Zeph: Cindy, are there thoughts of -- I'm thinking about our presentation this morning around the clinical protocols. And I'm wondering if any thought has -- or maybe there is something in place -- around family intake in terms of environmental exposures that could be coordinated and standardized in some way so that as we begin to look forward to not only the limited areas of environmental concern that we have right now but maybe a few promising areas of environmental influence, that we might have those data down the pike a little bit to refer to.

Dr. Lawler: I think that is an excellent question. The studies that are in place now, the epidemiology studies, are casting a broad net because we don't have a good idea of what the important exposures are.

If we can narrow down classes of exposure, then I think it's very feasible to design a short instrument that could be part of intake across clinical studies and it could be mined for

potential environmental influences with a larger group. We are doing exactly that in the context of Parkinson's disease. That is the case where we have more clues.

Dr. Insel: Can I follow up on that? I think this is very timely, this question, since we have been talking all morning about how we are about to launch a series of broad efforts to try to characterize this disorder and its many subtypes.

It seems to me that if we don't have something in place that we can integrate into that to get this kind of information, we will have lost a great opportunity.

I wonder if there is a way to even make this a priority for the group over the next few months before we actually start off on some of these other efforts. If it's happened in Parkinson's, it's happened in Alzheimer's, it's happened in other areas, what would be the impediment to doing it for autism?

Dr. Lawler: Having just gone through this with Parkinson's disease, where there are much more focused questions, coming up with agreement on how

to ask those questions and putting in place enough incentives for clinicians to include that and do the measurement or the assessment in a careful manner has been a major concern. I think it would show up here as well.

I think it's an excellent idea. I'm just not sure how feasible it is right now because I would want the intake to include questions about everything, everything that you have ever done or been exposed to or your mother or your father. And clearly that's not feasible to have a clinician that is really interested in language processing to add six hours of interviewing on exposures.

Dr. Insel: This isn't a field I know anything about, but I just wonder if there are other ways to do this using Web-based information collection, maybe involve Autism Speaks or someone else who has some interest in this and is going to be reaching out to 20-30 thousand families if there isn't an opportunity here that we ought to try to grab. And while we have many people in the room who will be involved with that, this may be a good discussion to have sometime during the day, maybe

in the hallway or at lunch or some other time.

Lee, you had a comment?

Mr. Grossman: The only comment I had was that it would be great to capture the data that I have been exposed to, at least, from the New Jersey study.

I am sure that the M.I.N.D. Institute also has numbers equal. The numbers that they have evaluated and the complexity of the evaluations and their intake are massive. And they are probably much greater than anything that the STAART or the CPEA centers have at this point.

Dr. Insel: Barry?

Dr. Gordon: I don't want to sound a cautionary note, but I do in a sense because obviously as you increase the number of things you are looking at, the number of spurious or possibly spurious associations goes up.

I wondered, for example, in that context. In the Berkowitz, et al., paper, the look that the PON --

Dr. Lawler: The PON-1, yes.

Dr. Gordon: -- the PON-1 and the head

circumference, was that a planned comparison or this was --

Dr. Lawler: Yes. I mean, that's the major enzyme in blood responsible for metabolizing that, the organophosphate pesticides and nerve agents as well.

Dr. Gordon: But, I mean, to look specifically at the parent status and then head circumference as a planned comparison that was one of their planned comparisons?

Dr. Lawler: That was, right, one of the measures.

Dr. Gordon: Very nice.

Dr. Lawler: And this is the first bit of data coming out of this cohort. The cohort is going to be followed over time. You know, they don't know what this difference in fetal growth may mean for further development or cognitive development.

It's all going to be followed up. That's just the first bit of information.

Dr. Insel: Thanks.

Shari?

Ms. Chase: Hi. My name is Shari Chase. I am a

mother of an eight-year-old autistic son. And I'm the Maryland representative for Unlocking Autism. How are you?

I applaud you for the environmental study. I personally feel, as well as my children's doctor, that that is probably the key to what can really assist stopping or the increase in our rising numbers of autism.

I want to ask you this. You had said there is no way to go backwards, that you need to move forward. Well, my son was poisoned by arsenic. And his doctor, Dr. Richard Layton, -- I believe he is very well-respected in the autism community -- decided after that he would look into all of his patients that the parents claimed had mercury poisoning or really felt that something happened overnight to them.

Interestingly enough, he started doing heavy metal screens to them. He has incredible amounts of research and data that has been done over the past five years.

Why can't you go to doctors that have been collecting that type of data and look at what

occurred? You would be able to find out when the person was exposed, most likely. You can do hair samples. You could do nail samples. You can look again at the research. And then you can follow if someone has been chelated if there has been a difference.

I really feel that you can go backwards. And then you could take that information and see how that child has developed over the past five to four years. I think that would be very helpful.

I guess the other thing that I wanted to ask you, are you going to be looking into heavy metals? One thing that really frustrates me is that I advocate. I don't lobby. But I come from a big group of friends who are lobbyists.

And I also coach. And I try to tell my kids when they're playing soccer you don't kick it to a goalie when you kick your ball. You hit it to the side. And eventually, if you keep on kicking it to the goalie, you're going to lose the game because you run out of energy. The game ends.

I feel that vaccines are very, very important. They can't be stopped. However, when you look into

the research on possible mercury poisoning, if you keep on pressing towards vaccines, vaccines, instead of looking at other sources of mercury and considering that the shots are good, you keep the vaccines in there, but that the mercury could have injured somebody and you look at the other heavy metals that have similar types of characteristics that would damage a child, then, instead of constantly having the pharmaceutical companies and the other lobbyists trying to argue the fact that it couldn't be, if you just say generically that there are heavy metals that could affect children and put more emphasis on researching that and possibly something could be done and we could stop other people from having the effects of heavy metals. And we could also look more into interventions that could help the people that have already had toxicity from it.

So what kind of research have you done with that?

Dr. Lawler: Wow.

Ms. Chase: You know, I have to say one other thing. When I started my pharmacology program, I

still remember my professor saying, "You're coming into a guessing game. There is nothing exact with science. And, remember, you must make us a promise that common sense always has to overrule."

And in this case, I think common sense can look at what has happened to these children. And we have to put emphasis there.

Dr. Lawler: So I'll say two things that I hope will be encouraging to you. The first is that I believe the UC-Davis Center in their large CHARGE study is doing a fairly complete analysis of various metals. Isaac, nod your head. Yes? Yes.

Dr. Insel: And Isaac will be talking just after lunch.

Dr. Lawler: Right, after lunch.

Dr. Insel: Yes.

Dr. Lawler: And, more importantly, you're right. There is a huge amount of data out there collected by clinicians. And the best use for these data are to generate hypotheses.

It's difficult to use them in any kind of confirmatory or mechanistic sense just because the issues of what is the appropriate control

population and what kind of selection bias do you have with individuals that came to this clinic in the first place are probably not a representative sample. Their friends are not good controls.

There are some very systematic methods to evaluate risk factors that are very onerous because they require putting in place the infrastructure to support a population-based study so you can get the right control groups and you know that you have a representative sample. I think Isaac can tell you how long it took just to set up that UC-Davis CHARGE study. That took about two years just for the IRB part of it.

So studies are in place. And the kinds of hypotheses that are popular that we have heard about I think can be addressed with the studies that we have now.

Dr. Insel: Well, thank you, Cindy. It's time for us to break for lunch. We will reconvene here at 1:30. And we will hear at that point from Dr. Isaac Pessah further about environmental influences.

[Whereupon, at 12:32 p.m., the foregoing

matter was recessed for lunch, to reconvene at 1:30 p.m. the same day.]

Dr. Insel: We're going to begin the afternoon session. Continuing with the theme of Environmental Health and Disease Prevention, Dr. Isaac Pessah is going to join us.

Dr. Pessah received his BS degree from Cornell University and a Ph.D. in Toxicology from the University of Maryland. He is a Professor of Toxicology and Director of the NIEHS Center for Children's Environmental Health.

He was, for five years until recently, the Chair of the Graduate Program in Pharmacology and Toxicology and he has been a member of the Center for Neuroscience in the M.I.N.D. Institute at UC-Davis.

Isaac, I think -- well, I think we have now a quorum. Why don't we go ahead and get started.

Dr. Pessah: First of all, I'd like to thank the IACC for a generous invitation to give you an update on our progress at the UC-Davis Center for Children's Environmental Health and Disease Prevention.

We're one of two centers funded from our wonderful sponsors, the National Institute for Environmental Health Sciences and the U.S. EPA that actually focus on autism and possible gene-environment interaction, the other center being at New Jersey.

We also are funded -- and many of us in this program in the center are part of the UC-Davis M.I.N.D. Institute. And so when one looks at the structure of the Center for Children's Environmental Health, it might look a little bit familiar to some of you in that it is probably what we would consider a mini- phenome, if you will, in that we have been trying to bring together scientists from diverse backgrounds, neuro-anatomists, cell biologists, immunologists, analytical chemists, people that wouldn't normally be talking to one another.

And the bottom line is that one needs such a multidisciplinary approach to tackle the very, very challenging issues in gene- environment interactions with autism.

And so I'll just briefly go through how our

center is organized. We have an Epidemiology Program, which is essentially an environmental epidemiology, which is designed as a case control study.

We are recruiting families through the Regional Centers, the California Regional Centers. And the samples and data generated by the CHARGE study are distributed amongst three cores. These cores include a state-of-the-art analytical core for both environmental elucidation of environmental markers such as poly brominated diphenyl ethers, PCBs and heavy metals, amongst others, immunological signaling where we actually take peripheral blood cells and look at their responses as well as molecular biomarkers which involve both genomic analysis and transcriptome analysis.

We also have a core program to develop animal models in autism, especially those involving gene-environment interactions that might be relevant to autism or at least development of social behavior and one that looks at possible molecular mechanisms.

This is all brought together through an administrative core that is overseen by an external advisory committee, science advisory committee, as well as our community partners.

So Davis is a particularly unique place in that it has several different facets of both toxicology and neurobiology to bring together to study children's environmental health.

These include, of course, the M.I.N.D. Institute and the School of Medicine but also the Interdisciplinary Center for Plasma Mass Spectrometry which has really given us a boost in our metal analysis, this NIEHS Center for Environmental Health Sciences, the Center of Excellence, the Superfund Basic Research Program funded through NIHS and EPA, as well as a Primate Center and a Mouse Center, which essentially is devoted to developing mouse models, especially transgenic mouse models.

So this is a daunting task. Most of you are saying, what is he going to tell us? And I'm trying to keep you awake here because I know it is after lunch. What is he going to tell us about

what is causing autism? And the problem is that it is a very, very complicated issue and one, when I realized what I was getting into I almost decided to lose sleep over it, but it's gotten better, believe me.

Of the 53,000 commercially important chemicals that we commonly use today, a National Toxicology Program Report back in 1992, and it hasn't gotten any better, essentially says that we don't have sufficient information on 49,000 of these for adequate toxicity testing.

Now one would think that pesticides, which are more highly regulated, would have a better information database. And, in fact, 64 percent of them lack adequate data for risk assessment.

Now I bet many of you don't know that it is just three or four years in that we've actually begun to require neurodevelopmental toxicity testing on pesticides. So one would think that this data exists before these pesticides are marketed, but in fact, some data is present but most of the data needed for adequate risk assessment, especially in kids, is lacking.

And one can go further for cosmetics and food additives. Okay? So all in all, there is a lot of work to do in trying to do better risk assessment based on actual data for all of these compounds.

So what's our overall hypothesis at the Center for Children's Environmental Health? Well, we know that autism has a genetic component. It is a disorder which, in fact, has probably 10 to 20 defective genes in any single child that goes on to develop what we call a dysfunctional phenotype or autism.

It should not be a surprise then, because this has been known in the cancer field for many, many years, that repair mechanisms often times can mitigate the effects of the genome defects and mitigate the dysfunctional phenotype.

Epigenetic factors, environmental factors, whatever you would like to call them, are clearly interacting with the genes to influence not only additional gene defects such as -- well, we've known in cancer for a very long time if you have a genotoxic agent, it's now screened out right at the very beginning of the pipeline in drug

development or in pesticide development.

So that's one area when we came up with the Ames test for mutagenicity, if a compound comes up positive, it's not processed further for general environmental dissemination.

However, we also know of environmental factors that are promoters, things that play off of the genetic weaknesses to, in fact, not only affect and exacerbate these genetic factors but also can impair repair mechanisms. And this leads to either an increase in the prevalence of measurable defects, dysfunctional phenotypes, or, in fact, making that phenotype worse.

And so the CHARGE Study, which is the childhood Risk from Genes and the Environment is a case-controlled study and right here I would like to thank our parent participants and our child participants because without them, this study could not be possible.

And, in fact, this slogan, "Be in Charge" has served well because the families that come into the studies are not only looking for solutions to what might be causing the problem in their kids

but also have a lot of hope that we will find something because if I step back for a second, the genetic disorders we have a long way in going before we can remedy these problems.

Certainly we can intervene pharmacologically. If we can identify environmental factors which exacerbate these problems, then we can get rid of them.

So the CHARGE Study is, in fact, quite elaborate. It's, as you can see, very well staffed. We have our principle investigators, Irva Hertz-Picciotto, which is an environmental epidemiologist, Robin Hansen, a pediatrician, and Lisa Croen, which is an autism epidemiologist.

We're doing environmental exposure questionnaires. We're getting a plethora of data from medical records and clinical records. But we're also doing our own testing in the clinics.

And now we even have a recruitment where we're trying to get our -- the study is divided into three groups. We have children with autism, children with developmental delays without autism, and children that would be considered normally

developing. And here's we've now just stepped up our recruitment of the MR/DD as well as the normally developing cohorts.

So how are we doing? You have to realize that we got started in late 2001. The M.I.N.D. Clinics weren't built at that time. They didn't get completed until July of 2002. But that was okay because it took us that long to get a 900-page IRB through the state, through the UC-Davis people, as well as down at UCLA. So it was a monumental task which the CHARGE people really should be commended for.

But as of the last count, when we go to the database, the number of clinic visits have been 667 and they fall out into these kinds of numbers for enrollment, parent module completed, child module completed, both modules completed, the exposure questionnaire, and the family visits. So in other words, we've had 667 families come through the clinics at this point.

We've gathered a significant amount of biological tissue from these families including the fathers, the mothers, the index child, as well

as one sib. These are the requirements for entering the study. What's really interesting is that the mothers are much better at giving blood than the fathers. I wonder what that means.

So what are some of the findings? Much of what we've collected remains unanalyzed. However, we do have some sort of midway-point types of analyses that have been drawn out from some of the questionnaires. And this slide summarizes some of the findings for sleep patterns and development of children with autism. And I pulled this one out because it is one that is pretty far along but also one that might fit into this issue of gene-environment interactions.

And so if we look at our findings, we see that in terms of the association between delayed cognitive developments and increased daytime to nighttime sleep, in fact we see essentially the same thing that has been previously reported.

However, the study goes on to ask questions that have not been previously addressed. And so we find that there is a resistance or sensitivity to environment or direct environment at bedtime,

which is correlated with cognitive impairments in development in our CHARGE sample.

Adaptive development in sleep patterns also have not been investigated before and have been investigated in this study. So if we were to conclude, essentially we need to do more because it is unclear whether autism exacerbates sleep problems or sleep problems make autism symptoms worse. But clearly they are related to one another.

Both sleep disturbances and autism are consequences of a common unidentified cause or causes of cognitive adaptive delays. So essentially if autistic kids can't get normal sleep patterns, they will have at least as one outcome cognitive and adaptive delays.

So let's go back and say could there be environmental factors in the homes that could exacerbate this kind of condition? And so let's go back to these pesticides and ask are there any pesticides that we know of that are cytotoxins?

Well, we don't have to go very far. For over 35 years, this litany of chlorinated hydrocarbons

have been used in the United States and elsewhere, which include things like heptachlor, chlordane, dieldrin, kepone, and toxaphene.

And here I give you the dates of which they were banned. So they were used right up until these dates and then they were banned for two reasons. One, they caused seizures. And two, they never break down.

In other words, these guys cause seizures because they block the GABA-A receptor pore which is the major receptor that is involved in regulating the excitability of the nervous system. It's the major inhibitory neurotransmitter receptor. It's an ion channel that conducts chloride.

If these compounds get into the CNS and block the GABA receptors, in fact you will block chloride influx and you will have a hyper-excited or seizurogenic state.

Well, it's a good thing that these were eliminated from use because essentially more than 55 years later, wood treated with any one of these products is still repelling the insects. In other

words, these things last for a very long time.

Lindane is still a controversy. Still being used for head lice as a last resort and for a treatment of scabies. At least this is one of the things that the manufacturer is trying to push for now. So these are of historical importance. Most people don't have these things in their house unless they're treating their kids with lindane. So we think we're safe.

However, if you look at a new class of insecticides known as fipronil, these are pesticides that, again, have been biorationally developed to target insect GABA receptors. And during that biorational development, the company compared the insect receptors' affinity for these compounds with the affinity for the typical human GABA receptor. And the finding was that, in fact, there was over a hundredfold difference in affinity favoring the insect receptor. Therefore, they must be safe.

Well, it turns out that because of this insecticidal ratio, if you will, fipronil and other 4-alkyl-1-phenylpryazole compounds are now

being applied at the rates of 800 tons, at least, greater than 800 tons. This was a value back in 2000. These are agricultural products.

But if you look down here, there are two products, and probably more, that are actually in everybody's home, Frontline and Chipco Choice. These are compounds that are fipronil formulated for home use.

Why is this important? Frontline doesn't block the pore. It's a noncompetitive inhibitor of the GABA receptor. So if it is bound to a GABA receptor, GABA won't bind. This channel essentially will be taken out of commission.

Now how does that relate to autism? It turns out that -- so that's this statement right here -- why is this stuff relevant to autism? I think you're all asking this at this point.

One of the hottest regions linked to autism, and one that has been replicated in several labs, is a problem with 15q 11-13. This region of Chromosome 15 codes for several GABA-A receptor subunits, including the beta3 subunit, which is involved in the fastest inhibitory synaptic

transmission in the mammalian nervous system.

A deletion mutation in this gene is thought to be involved in Angelman syndrome and Prader-Willi syndrome, both of which have autistic-like problems. And there has also been a link, a possible link, between insomnia and a mutation, a specific mutation within the beta3 gene.

And so here is this region of Chromosome 15 and you can see right here upstream of this maternal expression domain are the three GABA subunits that could be targeted by these very persistent chlorinated hydrocarbons. But remember they're not in use any more.

What about fipronil? Oh, one thing I forgot to mention, too. The GABA-A beta3 subunit is also regulated by another gene that has been linked to autism, MECP2. And Janine LaSalle, from UC-Davis, reported at IMFAR this year that a deficiency in MECP2 expression, this is a transcriptional factor, in cerebral samples seems to be associated with a pronounced down-regulation of two genes, the GABA-A beta3 receptor gene as well as UBE3A, both of which are in this hot spot for autism.

So I forgot to mention this part here. Why is this relevant? Well, it turns out that the initial screen that made these compounds appear to be safe may not be -- well, probably true but may not be telling the whole truth. A recent study just published by John Casida's group at Berkeley essentially has shown that the structure activity studies show that fipronil has a very high binding potency to the human beta3 GABA receptor.

In other words, if you compare the affinity of this noncompetitive inhibitor to the beta3 homopentamer, compare it to the insect receptor, it can't discriminate. They're both as high affinity targets. So we've lost the selectivity at least as far as the beta3 receptor is concerned.

Furthermore, if the beta3 receptor is being down-regulated, and this is about a tenfold down-regulation according to Janine, then one could imagine that you could, in fact, test the hypothesis.

This is a hypothesis-generating scenario here where if you have down-regulation of GABA-A receptor beta3 subunits because of a down-

regulation of a transcriptional promotor, then GABA receptor blockers that, in fact, target the beta3 as well as they would the insect could, in fact, exacerbate any problems generated by having this defective gene. This is a testable hypothesis and one, I think, should be tested.

So let's get back to the CHARGE Study because I want to give you some of that information. We have blood samples for immunology so we're looking at cells for T-cell activation, and I'll show you a little bit of that data, plasma/serum samples for antibody-specific immunoglobulin testing.

We're looking at general immunoglobulin in the blood, including IgGs, IgEs, and so forth. We've now got 132 mRNA samples on the Affy chips, which is going to look at some 30,000 genes to see if we can subcategorize our CHARGE kids. We are generating serum for genomic profiling, serum for lipid profiling, whole blood for metal analysis, and I'll show you some of this data, and then also hair analysis using a very, very interesting method.

So I'm going to actually just skip through

this but you can imagine that keeping track of where all these samples are going gets pretty hectic. And so we've developed a system where we can track every single microliter of every single sample that moves through the center. So we know who has what in the freezer. So it gets pretty complicated.

So let's take a look at our analytical core. This is run by Bruce Hammock, who has not only made this a core for service, so to speak, but is also developing state-of-the-art methods for analyzing proteomics as well as organic molecules from xenobiotic sources in very, very small aliquots of blood and urine.

We can look essentially at 150 -- 100, 200 microliters of blood and get some meaningful data. And so these are the types of instrumentation that he uses. And they range from sensitivity in the high nanomolar to high micromolar.

So one of the hypothesis that's been put forth is that kids with autism have morphine-like metabolites in their urine. That was published a year or two ago. And this was based on liquid

chromatograph-type analysis.

And so what the Hammock group did was essentially develop a mass spectrophotometric approach, which is much more quantitative as well as much more sensitive to test this hypothesis with the CHARGE sample. And in particular they developed this assay to look at six urinary peptides which include gliadinomorphin and beta-casomorphin, both of which were reported to be elevated in kids with autism.

And this is just the standard curve showing that we can detect 100 nanograms per mL very easily using this method. These were urine samples that were spiked with each one of these types of compounds. And so a very sensitive, very unequivocal way of identifying these morphine-like metabolites.

So what's the answer? Well, the answer was sort of discouraging or encouraging depending on how you want to look at it. The analysis of the first 77 first morning urine samples for these urinary peptides essentially indicated that all the samples were age and gender matched so there

was no issue. Because this is a case-controlled study, we can do that.

Essentially, the bottom line is that these neuropeptides were not detected above the limit of detection for any of the samples we looked at. So this, of course, requires further study with maybe a larger sample set. But the initial, and I think rather convincing, indication is that maybe this opioid peptide hypothesis doesn't stand up to scrutiny.

Let's look a little bit more at environmental agents. Obviously mercury has been brought up several times here. And so one wants to be able to say well, from molecules to childhood dysfunction, what is the role of mercury in developing neuro-developmental disorders like autism?

Well, we sort of fixate on one form of mercury, thimerosal. But essentially we know that there are several sources of mercury that eventually make their way into children. These include everything from the mercury amalgams in the moms to, of course, the childhood vaccines with thimerosal, now flu vaccines still being a

problem because of the thimerosal, several consumer products also are still preserved with thimerosal. So vaccines weren't the only source of thimerosal.

Now what is unique about thimerosal is that it is ethyl mercury, not methyl mercury. But there are a large number of environmental sources of exposure to mercury, mercury vapor, fish consumption primarily results in exposure to methyl mercury as well as other foods.

Now other foods is a big question mark here because we haven't paid as much attention to general foods that may contain mercury relative to our concern with fish consumption mercury. And I want to point out that mercury is not always accounted for.

There are six chlor-alkali plants still in operation in the United States that use mercury catalyst to convert starting materials into acids and bases that are then widely distributed throughout food and agriculture.

Twenty to 100 tons of mercury per year are unaccounted for by these plants. That doesn't mean

that they are going out the smokestacks or out through the water stream. This actually means that we don't know where it is going.

So the question then comes available because I've been asked this, some of the acids and alkalis from these plants end up in processing sugar into high fructose corn syrup. Do we know that we don't have minuscule contamination as mercury leaves the plant through these acids into one of the major foodstuffs in society today.

I wish I could give you an answer. We don't know. I've gone and asked lots of people. The answer is, we don't know.

So how do we analyze for mercury at Davis? We use this inductively-coupled plasma mass spectrometry instrument which essentially allows you to look at 20 or 30 different metals simultaneously in a range that can span parts per trillion to parts per thousand. So for each blood sample, we can get a fingerprint of what 20 to 25 metals are doing for that sample.

And so here is just an example of such data. Here what we're looking at on this axis is the

magnesium variation in these blood samples. Each one of these is a different child. And on the X axis is the level of mercury. Both of these are in nanograms per mL.

And one of the things that impressed Peter Green, who is doing the analysis, is that well, you know, magnesium is a highly- regulated physiological ion and amongst the children that we've looked at so far, it's very tightly packed across a very, very narrow range.

However, if you look at mercury, the levels, in fact, represent those that were reported in NHANES, so this population isn't all that atypical except that when you look at the distribution of metal levels in these kids, they can vary by, well, from hardly detectable to up above the 50th percentile based on the NHANES analysis. And so there is a huge variation in metal content in our CHARGE kids.

And so now Irva is doing some meta-analysis on how these fall out in terms of IQ, severity, regression, and that sort of thing.

But this is the distribution plotted in a

different way. Percent of children as a function of mercury levels in the blood. And you can see that there is nothing remarkable about the distribution. Most kids have very low levels but there are a few kids that are quite high. And so the question is who are these kids and what is their problem, if they have any.

The other thing we're looking at is hair because mercury in the blood only gives you a snapshot. Hair, on the other hand, gives you a temporal sort of timeline of what has happened depending on how long the strand is. And the way we go in here is we go in with a laser that will drill a very, very small 30 micron diameter hole, will get rid of the surface junk, drill into the hair, and then that hair is essentially pyrolized and analyzed by atomic adsorption.

And so we could do this every hundred or so microns down the hair shaft and get a history in time in terms of mercury exposure. Okay? And so this is data that is still in progress.

So - thimerosal. For ethyl mercury there is very little data. Most of our knowledge about

mercury is from metallic mercury and methyl mercury. And so one assumes that we can hypothesize or extrapolate from metallic mercury and methyl mercury to ethyl mercury in terms of risk assessment.

And I think these have been touched upon earlier so I'm just going to put them up there. But one of the factors in suggesting that the amounts of ethyl mercury in the vaccines should not be of concern is that, in fact, there are several studies -- well, at least two studies that have come out indicating that the half-life of ethyl mercury in the blood is much shorter. In fact, three times shorter than methyl mercury.

So if we were to use methyl mercury as a risk assessment, then ethyl mercury would certainly be within those guidelines. Well, that was true until about a few weeks ago when Brubacher and colleagues published a paper in Environmental Health Perspective, and I don't have time to go into the details, but essentially what they found is even though the peak concentration of IM mercury in the rhesus macaque is the same as oral

mercury in the same animal, in rhesus macaque, the elimination of ethyl mercury is, in fact, about three times faster from the blood. The problem is that given their exposure protocol, which tried to mimic that of childhood vaccines, their conclusion was that proportionately, there was significantly more of the ethyl mercury as metallic mercury in the brains of the macaques relative to methyl mercury.

So in other words, even though the elimination is faster, the distribution to target organs is more efficient. And so their conclusion was that mercury, blood mercury, may not be a good indicator, in fact that it underestimates the risk of adverse effects on the brain of ethyl mercury. And, therefore, methyl mercury is not a suitable reference for risk assessment.

So what you don't know could come back with data to suggest maybe more study is needed. And, in fact, that's what they suggested.

And so what do we know about the cellular toxicity of thimerosal? We certainly know a lot about the immune effects of methyl mercury and

sort of the neurotoxic effects of methyl mercury at the cellular level. But very little is known about ethyl mercury as thimerosal.

And so the old school about mercury toxicity is that essentially it is a non-specific biocide - that just about every protein in the body contains thiol groups, cysteine residues, and these are in fact a target for mercury.

And so one would probably need a very large level of mercury to start effecting critical macromolecules. Well, a new concept that is emerging is, in fact, that there are critical macromolecules that utilize cysteines within their structure for redox sensing functions. And this is significant because these proteins, in essence, use oxidation reduction chemistry to promote ongoing functions, signaling functions.

So if you take this chemistry and say if you had very, very low levels of mercury that don't change the bulk thiol status of a cell or an organism, could these be preferentially targeted? And, in fact, there is evidence that they can. Why? Because these cysteines are 10 to 100 times

more reactive toward mercury and other self-hydroreagents than, in fact, the general population of cysteines.

And so when one considers critical macromolecules in terms of how mercury can affect function, this is a very important new piece of information that we need to take into account.

So what kind of enzymes are we talking about? What kind of proteins are we talking about that utilize redox chemistry? They include enzymes involved in oxidative stress or management of oxidative stress, including metallothionein, glutathione-S- transferases, and glutathione peroxidases, all of which are highly sensitive to self-hydromodification.

They also include, and this is where I want to loop it back to proteins that are involved in transcriptional regulation and repair. This is a very hot area in gene regulation right now. And I bring you back to MECP2 which, in fact, belongs to a family of proteins that contain the CxxC motif, which is now recognized as a redox sensor which is involved in these redox regulation processes.

Remember that MECP2 is, in fact, the protein that is down- regulated in autism. And as a consequence, is thought to down- regulate GABA receptor beta3. It's not the only family, though. There are antioxidant response elements, AREs, as well as cell- signaling molecules such as calcium channels, including the microsomal calcium channel that we're studying in my lab.

And so these are the family of proteins within the MECP2 family which contain these hyper-reactive cysteines involved in transcriptional regulation.

The other protein, this is a rather large protein. It's about 2.5 megadaltons. It sits across the endoplasmic reticulum. It contains a redox sensor. If you put one point mutation in these 5,000 amino acids, which is just one subunit here, in essence patients seem totally normal until you expose them to a xenobiotic. And then they have a very short time to live because they develop a disease called malignant hyperthermia.

This has been very well studied now. But this is an example of a protein which, upon mutation,

may lead to what would be normal phenotype when challenged with an external environmental trigger will cause a very drastic phenotype.

So I've got -- I guess I can still go -- so we talk about critical macromolecules. What about critical cells? If we expose children to thimerosal through IM injection, are all cells going to have an equal shot at being disrupted? Well, if we look at the CNS, the Brubacher paper suggests that at least a high proportion or some of that mercury is going to get -- forget the high proportion, but some of that mercury is going to get to the CNS.

However, what about the peripheral immune system at the site of injection? Certainly we can talk about T cells, B cells, and macrophages, but one of the areas that we're very interested in is, in fact, the primary antigen-presenting cells known as dendritic cells, for several reasons.

One, they are at the site of injection. Two, they actually use redox sensing to mature and to extravasate to the lymph nodes to communicate with T and B cells. And three, they contain our protein

of choice which I just showed you which is called the ryanodine receptor which, in fact, has redox sensing capabilities.

And so for these reasons, we decided to look at the sensitivity of dendritic cells to thimerosal, methyl mercury, and ethyl mercury. This is a dendritic cells isolated by Sam Goth in the lab. And you can see it is a very pretty cell. It has these wonderful dendritic elaborations almost like neurons would. And all of this surface area is used to communicate information to T and B cells, primarily T cells.

So they are antigen-presenting cells, so they take up antigens and present them to T cells. They are a very small fraction of the circulating cells. They only account for about .3 percent of the cells in the circulating blood. But don't underestimate their function. One DC, dendritic cell, can activate at well over 250 T cells in the lymph nodes once it matures.

So -- and again, maturation is tightly regulated by redox environment. And so we asked the question -- this is just showing you the life

stage of a dendritic cell. So obviously dendritic cells, once they mature, they receive an antigen, perhaps at the site of injection or a site of injury. They extrapolate through the lymph ducts to the lymph nodes where they then present to T cells.

And then the T cells then proliferate through clonal expansion with the information that was given to them by the dendritic cell. And so dendritic cells play a pivotal role in immune activation.

So the first thing we did was we just looked for the dose response at what would cause apoptosis, a naturally-occurring process in these cells in response to thimerosal and ethyl mercury?

And what we found was rather surprising in the sense that we expected a dose response relationship up in the micromolar range and what we found is that we could find caspase-dependent apoptosis with 20-hour exposure to thimerosal as low as 100 nanomolar.

The dose response shows that ethyl mercury and thimerosal are essentially equipotent whereas what

we call thiosalicylate, the part that doesn't contain mercury that is metabolized away from thimerosal has no effect.

And so this is very interesting in the sense that by reducing dendritic cell numbers at the site of injection may have limited effect since these cells are going to die anyway. But on the other hand, since they're so rare, it may have a consequence on immune function.

So we actually wanted to look if the target proteins that are redox sensitive are present in the dendritic cells. And what we found was actually not so surprising in that there was some functional evidence of this in the literature already.

But that dendritic cells not only expressed that huge calcium channel that is present in the brain and in skeletal muscle, we call it RyR1, but they also expressed the smaller genetic-related protein, the IP3 Receptor 1, which is also present in the microsome.

And if you compare the distribution of these two proteins, they are very distinctly

distributed. Where the RyR1 shown here in red -- actually these colors are reversed -- are at the base of the dendrites like you see here.

And so the question was --

Dr. Insel: Isaac, we're going to need to wrap up pretty quickly --

Dr. Pessah: Oh.

Dr. Insel: -- because we're just about out of time. So take maybe another three minutes?

Dr. Pessah: Yes, I'll be finished in three minutes.

So clearly these exposures to thimerosal disrupt the calcium signal emanating from these channels and can result in disregulation of IL-6 secretion in these cells.

More importantly what we found was that based on the transcriptome, we looked to see if, in fact, thimerosal can interfere with invariant chain, which is very important in maintaining or at least preventing initiating autoimmune responses from these dendritic cells.

And, in fact, invariant chain is down-regulated in thimerosal- treated DCs and these DCs

then can bind more peptide at their surface because of -- as a consequence of this.

Why is this important to autism? Well, Judy van de Water, analyzing samples from the CHARGE Study, essentially has identified that the autism samples are, in fact, very, very poor responders to bacterial toxins such as diphtheria, tetanus, bordetella.

So in other words, the kids with autism compared to the general population and compared to their sibs, unaffected sibs, are somewhat hypo-responsive to bacteria antigens. And so clearly this implicates immune problem in autism.

And I'm going to have to go past this. Our animal models are showing up some really interesting things. Obviously not enough time -- way not enough time.

But let me lease a take-home message. We often are asked the question what is causing autism at least in terms of environmental factors. We certainly have been asking this about the genes. And maybe a better question is not what is causing but, in fact, what types of environmental stimuli

are causing the autism phenotype to either be exacerbated or taking a child that would otherwise be outside spectrum into the spectrum.

And so this model here is our sort of working hypothesis that environmental factors through several hits probably exacerbate genetic problems in autistic children to lead to an exacerbation of the dysfunctional phenotype.

I thank you.

[Applause]

Dr. Insel: Thank you. Although we don't have much time, I think we should take a minute if there are questions.

Can you clarify one thing which is coming up in the literature? The distinction between organic and inorganic mercury.

Dr. Pessah: Yes. Organic mercury either has methyl or ethyl or dimethyl coordinated with it so it actually has carbons associated with it, carbons and hydrogen whereas metallic mercury exists as the metal form, Hg+2.

Dr. Insel: And is it the organic form then that is more toxic? Or is that clear?

Dr. Pessah: As this statement would say, organic forms of mercury are much more bioavailable and therefore much more toxic than the inorganic. But that doesn't mean that inorganic mercury once it gets to target organs can't be toxic or at least disregulate.

And so this statement was made by Karen Wetterhahn who spilled two drops of dimethyl mercury on a gloved hand and died three months later.

Dr. Insel: Jim?

Dr. Hanson: You looked at DPT but how about MMR?

Dr. Pessah: We actually looked at that and at this point in the analysis, because again this is a meta-analysis, it doesn't obviously involve all the kids that we've actually looked at. But at the time we did this analysis, MMR didn't seem to be different - - did not seem to be different.

Dr. Insel: Okay. Thank you very much, Isaac. That was terrific. We're going to move on -- was there another question? Is it a question? I'm just concerned about time.

Audience Member: Two comments, one question.

Dr. Insel: I'll tell you what. Let's -- why don't we do this because I think there will be a number of comments about this towards the end of the day. If you can wait, we'll make sure there is time at the end of the day to -- and maybe even then can have some additional questions.

Isaac, are you going to be here the rest of the day?

Dr. Pessah: Yes. I have to be at the airport by six-thirty.

Dr. Insel: We'll let you get out by then. Let's move on. I'm sorry. I do want to make sure we have a chance to hear updates from all of the different programs that are going on. And Alice Kau will start us with the CPEA's.

Dr. Kau: Okay. I will provide updates on two ongoing activities. The first activities that I would like to update you on is about the CPEA Girls Network Project. This project plans to use available common measures data to examine social behavior differences in girls with autism as compared with case control boys with autism.

The study will test the hypothesis that compared with boys with autism of similar age and IQ, girls with autism display milder expressions of autistic symptoms. And this study will also examine the possibility that the severity of expression of autistic symptoms in girls relatively to boys varies by age or developmental level.

We are in the process of putting the data together to identify a final sample from all the CPEA sites. And then a plan for data analysis will be developed after that.

The second update that I would like to provide you is about the Baby Siblings Research Consortium. The annual meeting for the Baby Siblings Autism Research Consortium was held on April 1st in Washington, D.C.

As you may recall, the National Alliance of Autism Research and NICHD joined to form this consortium in an effort to enhance research with population of young children at high risk for autism, particularly the siblings of children with autism.

There are currently ten research groups across the U.S. and Canada following cohorts of infant siblings of children with autism. The main focus of this year's meeting was on ethical issues that emerged from baby siblings research.

Dr. Insel: Okay. Thank you.

Deborah Hirtz in terms of STAART Centers.

Dr. Hirtz: I'll be very brief because I know we're running behind schedule and José has more to say.

But I just want to remind you briefly that last time I talked a little bit longer about the different interventions -- all the different projects as well as the intervention projects that are going on in the STAART Centers. And those were two projects on early intervention for different types of behavioral interventions. One was dietary intervention and two were pharmacologic studies.

And all of those are in progress. They are recruiting very nicely. They are periodically reviewed by a data and safety monitoring board who hasn't found that there have been any problems with children who are enrolled in the trials and

any adverse effects. So they take some time to complete but they're marching on and doing very well.

The two pharmacologic I just want to be a little bit -- expand on a little bit more. And that is, the first one is the citalopram trial for children who have high levels of repetitive behaviors. And that trial is doing very well. It has recruited just about half of the subjects that it needs to and is going along nicely.

And the protocol for the second trial, which was fluoxetine for very young children to see if it will improve the developmental trajectory, has been approved by the data and safety monitoring board. They're working on some final touches for just a pilot protocol of this. And working on finalizing the protocol and the consent forms.

There have been multiple different iterations of the consent forms because these are young children. It's a difficult issue. And we're trying to be very, very careful about making sure that these are just the way -- include everything that they should. And I expect that this pilot study

will begin in a few months.

The only other update that I want to mention is that there was a very wonderful meeting in April in Atlanta where all of the STAART investigators got together for a scientific meeting.

So that meeting involved junior investigators. Each center brought some of their junior investigators. And there was basically two days of scientific exchange in terms of presenting what people were doing and time for groups to get together to talk about what their common interests were and what they have learned and common potential projects.

There will a STAART CPA meeting that will be in November but the past April was just for the eight STAART centers.

So I think that's about all that I'm going to say about them. And give the rest of the time to José.

Dr. Insel: Okay. Thank you.

Dr. Codero?

Dr. Cordero: I'm going to go up to the front.

Dr. Insel: Okay.

Dr. Cordero: Good afternoon. Wow, there's one person awake.

[Laughter]

Dr. Cordero: Thank you for the opportunity to talk with you today. And I would like to update you on two CDC activities.

First, to share with you the results of the autism listening sessions that CDC held last fall but also give you a brief update on the "Learn the Signs. Act Early" Campaign, the Autism Awareness Campaign that we launched with our partners this spring.

Given the limited time, I will not address surveillance activity at CADRE Centers. Needless to say, quite a bit of progress has been made and I think that for the next meeting or by the end of the year, we'll have some important data on the important problems of autism and other things.

Now let's go to the listening sessions. These listening sessions was something that Dr. Gerberding asked us to do. And to start with, we used the research agenda that was developed here

by ICC as the starting point. And where we tried to focus on what are the activities related to research that relate to CDC and that parents were concerned.

We held four sessions in Florida, California, Indiana, and New York. And I'd like to thank the Autism Society of America, Cure Autism Now, and NAAR, and also the M.I.N.D. Institute for helping us develop and host these sessions. Like California, we actually held the listening session at the M.I.N.D. Institute. And we will have a summary report that will be distributed to IACC soon.

Meanwhile, let me tell you about the major themes that emerged out of these sessions. And here you have some of those major themes. But let me tell you a little bit about the cross-section or cross-cutting issues that also applied across the themes. And I'm going to be talking about each of them separately.

But many, many parents were concerned that they were not being heard by the healthcare, educational, governmental, and research sectors.

And they pointed out that parents have critical insights in their child's functioning that could be helpful in achieving an earlier diagnosis, developing more effective interventions, and identifying fruitful areas for etiologic research. Their perception is that their views are often ignored.

While there is support for research to understand the causes of autism, there is also a sense of urgency that more needs to be done to help today's children with autism. Many of the parents that participated in the listening sessions expressed concern in terms of the government agencies and specifically the perceived lack of responsiveness to parents' concerns about vaccines and autism but also other issues.

With healthcare providers, the perception of lack of willingness to listen attentively in response to parents' concerns about the child's development and use alternative therapies that many parents believe offer some benefits. And with service providers because according to parents, specialized services are not adequately available

and flexible.

The parents also expressed strong concern about wanting this uniform definition of autism that would be used for federal, and state, and health education agencies. And that had to do more with the question of how in some states may have -- they cover autism in a different way than other states. And some healthcare insurance would cover it and then others would not.

They consider that this lack of definitions or differential definitions is really a challenge in obtaining consistent services across life span and because of the lack of uniformity.

They also expressed a sense of urgency about the need to acknowledge the high rate of autism reported in the United States and other countries. And that sense of urgency was coupled with frustration that not enough was being done to understand what is happening and why.

So let's just look at the major themes. There was a general recognition that genetics may play an important role in the etiology of autism. And that genetic research should be pursued. However,

there was also concern that genetic research to often is given priority over environmental research.

Listening session participants also recognized the importance of a consistent definition of autism for tracking and surveillance.

There was also interest in getting better data about subgroups of autism spectrum disorders.

Concerning treatment, there was a strong sense of urgency by many participants about the need for a cure or an effective treatment including further exploration of alternative therapies.

We heard from some who do not trust CDC's assurance of vaccine safety, especially in regards to vaccines and autism. Some offered suggestions for rebuilding trust including instituting and oversight or advisory board for guidance of autism research and the separation of vaccine promotion programs and vaccine safety program. We actually have done that. The vaccine safety group now resides with the Office of the Chief Scientist.

Also they asked CDC to accelerate the process of removing thimerosal from the vaccines and that

is actually CDC, FDA, et cetera, and the vaccine companies.

In addition, many participants would like CDC to continue to evaluate the safety of the immunization schedule, including the assessment of any interaction between vaccines and other exposures that includes vaccines.

In terms of public awareness, I'll come back to that in a minute. But let me just come back to that theme in a minute.

And let's go to the next slide. Parents of children who are effected by autism expressed the importance of having better practices and models for treating -- early identification and treatment of autism. Let me say that one of the impressive things is that although we were focusing the listening sessions to issues related to CDC, there was a great deal of concern both in terms of the diagnosis, the guidance given to parents, but also the whole issue of what are appropriate interventions.

And, again, in that theme, lots of concerns about the limited availability of specialized

services and the challenges for those that rely on Medicaid, particularly how difficult it is to -- it varies a lot from state to state on securing the services.

Insurance coverage is a major issue. And, again, it's differences from state to state on what's covered and the fact that in some states autism treatment is considered an educational service, therefore not covered, and it varies even so much.

Finally, the lack of services for adults and adolescents and it is the transition of adolescents into adults was also a major, major theme.

As I mentioned in terms of CDC's response, part of the steps we are working in trying to remove thimerosal. And let me say that basically now for the recommended vaccines, all the recommended vaccines for infants, they are available without thimerosal. The one that is remaining is an influenza. And for that group, there last year we purchased between six to eight million doses of thimerosal preservative free,

that it's just not sufficient to cover all children. And part of the plan for next year is to increase the amount of that vaccine.

In addition, for children five and older, there is a new vaccine that's a nasal spray, a co-adapted vaccine that does not contain thimerosal.

The second step on this process is to share response with other agencies and also with IACC. I think that there are many concerns that actually an important part is to share with you.

We are looking at ways to improve our communication with parents. And we will be looking at other steps that we'll share with you at the end when we have the report.

Let me just move on to the second aspect. And it's the "Learn the Signs. Act Early." We were very pleased with the beginning -- of the rollout of the Autism Awareness Campaign. And you all have heard about this so I'm going to limit my remarks to where we are.

First it was terrific that we launched the campaign the 21st of February. And that was done actually in coordination with Autism Speak and NBC

that actually had a week-long series of programs on autism. And we have actually distributed three million e-cards. Those are e-mails to healthcare professionals. We've reached about 50,000 physicians and nurses at conference. And we have distributed about 15,000 healthcare provider resource kits.

We have had a tremendous reach in terms of the -- through news media, through different programs. But also the broadcasting of the public service announcement but also we have distributed about 20,000 parent kits.

And our website is cdc.gov/ActEarly -- we have had over -- about 120,000 visitors to date. And the downloading of materials, we have records of about 30,000 documents being downloaded to date.

The CDC info, we are getting some calls, about 8,000 to date. And we have quite a bit of materials.

So this is just the beginning and I think that more needs to be done. But I think that we had a good start and with the campaign to continue through the end of the year and beyond.

So again, thank you for your time. And I'll be happy to answer any questions you have.

Dr. Insel: Thank you, José.

Questions?

Mr. Shestack: Yes, Dr. Cordero, the final PSA ultimately didn't use the word autism. And the autism groups who were supposed to be consulted pretty heavily all felt pretty unanimous that they wanted it. And yet -- and also they fought pretty hard and directly to get a Congressional appropriation for that campaign but yet the CDC decided not to take the group's advice.

So I wanted to know why that was and I also wanted to know if it is possible to have -- at some point get an accounting of how the appropriation, several million dollar appropriation last year from Congress was used on this campaign.

Dr. Cordero: Jon, thank you for the question. As you know, the process with developing the PSA actually started with the formative research and where we actually went to parents of children with autism. And we had actually about seven -- quite a

few of those -- and actually they were done all through in the ASA meeting. And when actually all that research -- and originally we started with that we need to talk about autism.

And what we heard loud and clear was -- from that research was if you start telling me about autism, I'm not going to listen. But actually what would really help in terms of getting doctors' and getting parents' attention is to talk about the early signs and talk about normal development and to look at development in the way that actually would get parents to go and talk with the doctor.

And that was the basis that the campaign was done. And this was discussed with your staff. It was discussed. But we are open. For next year if we want to have something that would have more autism, we certainly would work with you on that.

And if you want some specifics, I don't have the details on how every dollar was spent. But we'll be happy to share that with you.

Dr. Insel: Other questions? Comments? We have about five minutes before the next session and there are some people here on the side of the

room. So if you'd use a microphone please.

Audience Member: Sure. Dr. Cordero, I'd like to know what the status is --

Dr. Cordero: I'm sorry. I'm having trouble hearing you.

Audience Member: What's the status of the release of the Vaccine Safety Data Link Project to independent investigators? Given the IOM report that came out calling for that sharing of the information.

Dr. Cordero: Thank you for the question. And the answer is I don't know the answer to that question. I will be happy to ask folks in the Vaccine Program about it. Okay?

Yes?

Audience Member: I'll just do this. I'm not a scientist. I run a parent group. It's international. And the angst that I hear from our parents -- I'm the listener, I'm not the scientist. And I try to pass it on to other scientists who try and give me the right answers.

And I'm hearing from parents that they are very frightened as to whether or not their

children are going to be able to be in public school -- if they're afraid. They've already had autism occur in their families. They're afraid to have siblings inoculated but they can't put them in public school and they can't afford private school. And now they really can't get them in the private schools either.

So what do we say to these families who -- you know, they have no scientific backgrounds. They just have to kind of trust the pediatrician they've got. The pediatrician's offices now say if you will not have your child inoculated, you will not be allowed to have our services as your pediatricians. What can you tell us about that? And what should we do?

Dr. Cordero: So what you're asking is what do you with parents when the child does not get vaccinated and then are unable to get to school because the school --

Audience Member: Well, our parents are stuck with that dilemma. They know it is coming up. They know that it is about time for their child to start school. The child has no symptoms of autism.

But has a sibling --

Dr. Cordero: Right.

Audience Member: -- or a cousin or whatever with autism or an autism-related spectrum disorder. And they're terrified. They feel like they're being almost forced to do something that they think may harm their children.

What can we tell them? Where do we send them?

Dr. Cordero: I think the most important is to talk with your doctor. And actually I think that most pediatricians do have quite a bit of information about that.

Audience Member: What the pediatricians are telling our families are you either get the shot or you're not my patient any more.

Dr. Cordero: Okay. Actually some of the most recent things that ask the pediatrician I receive from the academy is precisely that is not the message to give to parents. But actually work with parents in the process of understanding the balance of the risk of vaccines and actually the benefits of vaccine. But not to say go away if you're not going to vaccinate.

And I just -- and that would not be an appropriate way to go.

Audience Member: We'll just send them to you and then you could maybe send them to -- I'm not being sarcastic -- to other sources of help.

Dr. Cordero: I'm happy to talk with parents about that. And I have done that many, many times.

Audience Member: Thank you.

Dr. Insel: Last question or comment please?

Ms. Dunkle: Thank you. My name is Margaret Dunkle and I'm working in Los Angeles County with a group around early identification and intervention for kids with disabilities and delays. This work started around autism. And where we came to was looking for high-quality development screenings for all children, which also pick up kids with autism.

I mean for example you can take the PEDS, the Parents Evaluation of Developmental Status online now and immediately flip into the M- CHAT for autism for kids of the right age. So one of the things, your staff has been very helpful. We've used your materials with our will building and

skill building efforts in Los Angeles.

But to really look at the issue of high-quality developmental screenings which pick up kids with autism before you might even suspect autism because they're seeing in research situations now you can spot some of these kids as young as six months.

So one of the ways that we've taken this is to really try to broaden the groups effected by getting at all kinds of developmental delays, disabilities, and learning issues, which catches kids with autism earlier than if you just do an autism- specific screening. And also builds a strong base because you're also catching a large group of other kids that need early intervention.

And I just want to say thank you to you and your staff for the materials that you have provided and the help that you've given to us in Los Angeles. Thank you.

Dr. Cordero: Thank you.

Dr. Insel: Okay. It's time to move on. The last two presentations are going to be from the FDA, a group we have not, as far as I can

remember, heard from at this committee.

The first is from Dr. Glenn Manheim, who is a child neurologist and child psychiatrist as well. He's been involved with autism research but most of all autism treatment for a number of years in private practice.

For the last three years, he's been a medical reviewer in psychopharmacology in the Division of Neuropharmacological Drug Products at the FDA.

He's going to talk to us about the heterogeneity of autism and implications for clinical trials.

Dr. Mannheim: Okay. I'm going to be starting on Slide 14.

Thank you for the introduction. My perspective is that of a medical reviewer at the FDA. My role is determined whether a drug which goes to market is both safe and effective. And that it works in the group of children that it is supposed to.

In this heterogenic, most complex of disorders, which is autism, getting a drug to show efficacy in the core symptoms of autism and to have an effective, acceptable safety profile is

probably going to be very difficult and should not be underestimated.

The first 14 slides pretty much show, you know, evidence reviewed, which people have gone over this morning, which shows that autism is a heterogenic group of symptoms from, you know, the classic cannas to one of lifelong deficient social skills or cognitive behavioral flexibility to variable neuropathological findings being described, the increase cell packing density, the dendritic abnormalities, cortical heterotopias, and, you know, abnormalities in minicolumn cells, which has recently been described by Dr. Casanova, so all again suggesting heterogeneity.

Multiple neurotransmitters have been suggesting of being involved in autism. Serotonin is the one that is probably, you know, has been known for a while. Increased serotonin in peripheral blood and response to SSRI in some symptoms of autism, glutamate, and GABA. The fact that multiple neurotransmitters are involved means that a drug which comes to market, it's going to hard to prevent just one neurotransmitters --

multiple neurotransmitters are going to probably have to be modulated which, again, is going to make it much more difficult to show efficacy again.

And, you know, autism as we've been seeing here, is not simple. The environmental -- probably environmental causes, it's a complex trait. And I guess the other possibility is, you know, that it may not be amendable to pharmacotherapy. It's something we all have to think about. And this is coming from the FDA that you may have to control and change the environment.

I mean one, you know, thought, just thinking about, which wasn't gone over is what is called, you know, a founder effect, a bottleneck effect where maybe our choices of mating and diminished selectivity which results therefor, which might have a role in autism.

Now the FDA has to show that a drug is -- the Food, Drug, and Cosmetic Act said we had to show substantial evidence of effectiveness from adequate and well-controlled investigations. Now what are -- the components of these was left up to

the FDA to decide. What was defined as substantial evidence, what was adequate and well-controlled, and more than one investigation.

Based on the FDC, the FDA wrote regulatory guidelines defining what is an adequate and well-controlled investigation. And in descending order of preference and the first two are the gold standard: placebo-controlled trial, a dose comparison, concurrent control, no treatment concurrent control, active treatment concurrent control, and historical control.

The minimum design features of a trial in autism are that it be randomized, double blind, and concurrent-placebo controlled. Safety information needs to be included to show that a drug is safe. And the Food, Drug, and Cosmetic Act said to include all tests reasonably applicable to show the drug is safe under proposed labeling. And that the results of such tests show the drug is safe under such conditions.

Special safety considerations for drugs to be used in children are we need to know what are the long-term risks associated with the use of the

drug. What is the effect on growth and development? A drug that reduces behavior may have an adverse effect on cognition, which might not be desirable.

And then again there's this tension between everybody wanting a drug to market as quickly as possible versus understanding the full safety of that drug. And that is a balance that has to be carried out.

Now what is needed to gain drug approval for a new claim? One has to clearly identify, define, and name the clinical entity and distinguish it from other clinical entities. And you have to show that you can establish efficacy for that indication. That is you really have to show that it works and reduces the core symptoms of autism.

And you have to show that it is safe. And this has to go into labeling showing the target population which you are identifying and advise the prescriber how to use the drug safely.

Types of clinical entities considered as indications are -- it can be a specific disease, for example a non-psychiatric disorder would be

congestive heart failure, rheumatoid arthritis, or in the psychiatric disorder, major depression, schizophrenia, or it could be specific signs or symptoms of a disease syndrome, for example acute agitation in schizophrenia, or it could be non-specific signs or symptoms not unique to a single disease or syndrome, for example pain or fever.

One must be careful to avoid using pseudospecific claims. For example ADD in autism or OCD in autism is something one would have to think about really carefully.

A pseudospecific claim is an artificially narrow claim through empirically based -- it's artificially narrowly defined. It usually serves to promote a promotional but not true advantage over another drug with the same action.

If the advantage only holds for that disease and no other disease, then it is truly specific. It is pseudospecific until proven to be non-pseudospecific. If you had a company that showed that an SSRI had a benefit of effect in depressed who were all Virgos, that would be pseudospecific.

Dr. Insel: Mr. Mannheim, could you just -- I'm

sorry to interrupt. But I'm afraid that some of us may be getting confused. Is the claim that autism is a pseudospecific claim and, therefore, wouldn't be a target for drug development that the FDA would be interested in?

Dr. Mannheim: No, I think -- what I'm trying to say is some of the features of autism may be -- depending on the specific features, may be pseudospecific. But I think that the core symptoms of autism wouldn't be.

Dr. Insel: Maybe you could give us an example of what would not be of interest for developing as a target?

Dr. Mannheim: I mean we'd have to take it on a case by case -- Paul, you want to jump in?

Dr. Andreason: That's okay. I think a good example of that would be something like insomnia associated with autism. Insomnia is a claim -- so if --

Participants: Can you use the microphone?

Dr. Andreason: Insomnia is a general claim that we grant. So if a company came forward that already marketed a drug for insomnia and said

well, we want to get an indication for the treatment of insomnia associated with autism, we would consider that a pseudospecific claim because it treats insomnia in various clinical settings.

And it wouldn't necessarily be a treatment for autism per se but for a symptom that might be associated with it. And that's something that we would probably not consider as a valid claim in the treatment of autism.

Dr. Insel: Okay. Thanks for that clarification.

Dr. Mannheim: Okay. What's needed for a particular clinical entity to be considered an acceptable indication for treatment? It should be accepted usually in the clinical academic community. There should be an operational definition. It should be a reasonably homogeneous patient group. And it should not be a pseudospecific claim.

Criteria for targeting nonspecific psychiatric science symptoms as indications, one would have a definition, what specific diseases that it might be associated with. One should use a commonly

accepted agreed upon instrument of measurement. One should show, you know, it should be equally responsive to treatment regardless of the context.

The claim should be supported in several disease models. Understanding at the pathophysiological level is not a requirement in psychiatric disease.

Some things to consider in autism study design issues are should it be a parallel versus cross over? Should one include different types of comorbidity, for example an Landau-Kleffner epileptic aphasia? Should it be a placebo controlled? What are relevant outcome measures? Should one look at short- term and long-term effects? Should one look at a fixed versus a variable dose? Should one look at pediatrics versus adult subjects?

There are pros and cons to a cross-over design. Generally we prefer a parallel design because it is usually much easier to interpret. Comorbidity, you know, as everybody has talked about comorbidity is very common in autism as it is in many other psychiatric disorders. And,

therefore, a reasonable goal in the early development is maybe start studying relatively purer subjects and during later development, study subjects including various types of comorbidities.

Design issues regarding comorbidity for autism, distinguishing autism-specific responses from comorbid responses, detecting differential autism responsivity on the basis of comorbidity, addressing autism response specificity. One should have autism- specific outcome measures that the drug should show that it is making a difference in the symptoms of autism, an exploratory analysis to look for correlations between response on autism measures and comorbid measures.

Detecting differential autism responsivity on the base of comorbidity, one should generally ignore comorbidity except for post hoc explorations. The consequences can only test the overall hypothesis. It is hard to salvage a negative study. Stratify on the basis of comorbidity. The consequence can test multiple hypotheses but would need increased sample size.

Are placebo-controlled trials needed in

autism? And there are really three issues, regulatory, ethical, and practical.

From a regulatory point of view, one has to be able to interpret the studies. And one has to know what is the cause of the disease in the absence of treatment. And how treatment is going to effect the disease. I'm not sure whether it is true if placebo response is a big problem in autism studies.

I guess one ethical issue is the use of placebo when existing treatments decrease irreversible morbidity or mortality. And I guess it is less problematic when there are no existing treatments. And I guess a practical issue is always, you know, recruiting patients for placebo-controlled studies.

Outcomes of interest, really these are the questions for you all. I mean what are the demands of interest? The symptoms measured? The functions which you want to measure? How best to address these domains? What do you want to have as your primary outcome? What do you want to have as your secondary outcomes? What is the long- term

efficacy of the drug? If you see short-term benefits, will it endure after, you know, the child has been on it for six months, a year? Are there delayed long-term benefits?

Those response information is useful to maximize the benefits and minimize the risks. What is the most effective dose to use? What age groups should be studied in autism? What mix of children, of adolescents, of adults? What is the status of adult autism? Is there a consensus? Is extrapolation possible from one to the other? In which direction? Stratification for children and adolescents, what age would one cut off?

And, you know, given how complex autism is, you know, my personal view is one would need responder, non-responder. One needs to understand why people respond and why people don't respond. What differentiates responders from non-responders? And can one not just see who succeeds but understand why certain children didn't succeed.

And to do that, one needs a big, carefully defined phenotype to do correlations. And

sometimes even though it is not recommended, one may need subgroup analysis to see whether there is something there. And then, again, that would have to be tested in a new trial.

Anyway, I'd like to thank Dr. Laughren, Dr. Andreason, and Dr. Casanova for their input. And that's all.

Dr. Insel: Thank you. I'd like to go on to hear the second presentation from Dr. Paul Andreason. Also the FDA, Dr. Andreason is one of the two psychopharmacology team leaders in the Division of Neuropharmacological Drug Products at the FDA and is one of the people who be involved with applications for proposed treatments for autism for both investigational drugs and for drugs that are already on the market.

Dr. Andreason: Thank you very much.

I'd just like to make a few remarks today about the different ways one can look at development of drugs for psychiatric treatments.

I'd like to compare it -- the drug development for autism primarily with our history with -- brief history of drug development for

schizophrenia, another serious and poorly-understood disease but one for which the medical treatments have been a bit more promising.

Let me first start off by talking about what we actually do at the FDA, which, for me coming from NIH and going to the FDA, was a bit of a mystery. So I will have to assume that it is a bit mysterious for most people.

We have authority to regulate the investigational exposure of drugs to human subjects prior to their marketing. And then prior to marketing, but as drugs do come for marketing, the initial approval for safe and effective treatment for something if it is a new chemical. And then finally when drugs are marketed, we look at applications for expanding their indications through new claims.

The authority for the FDA comes from the Food, Drug, and Cosmetic Act of 1938 amended. And I should say amended in 1963 when efficacy was actually added. The amended FD&C provides that drugs must be both safe and effective for the use for which they are approved. Now when I say in

1963 they were amended to include efficacy, prior to that I think most people were concerned mostly with safety.

Now we are an agent of the electorate administered by the executive branch and we may be modified through legislation. And later I'll tell you just how much we've been modified within the last 20 years and how that affects our day-to-day life.

Some of the things that the FDA does not regulate, I think under the broadest definition, we don't regulate the practice of medicine. For example we don't regulate off-label use of drugs and that's generally -- the off-label use of drugs is generally legal. And the reason I say generally is because I'm sure that there is an attorney in the crowd that could come up with an exception. But right off the top of my head, I can't think of an exception.

We don't regulate psychotherapy, rehabilitative medicine. We don't regulate requirements for professional licensure. That's done at the state level. We don't regulate

surgical procedures. And we don't regulate what the standards of care might be.

Now I have a bit of an indictment for the psychiatric community, and as a practicing psychiatrist it's a self-indictment. Some of the historical patterns we've seen with psychiatric practice and research that is a bit discouraging is that when it comes to psychiatric treatment, if people believe something works, then it will seem to work until proven otherwise.

If it seems to work for someone, then everyone will end up getting it. If it doesn't seem to work as we previously thought, then it seems that it is going to be used in greater amounts for longer periods of time. And that the scientific advances over the last 40 years have not appreciably changed this pattern.

[Laughter]

Dr. Andreason: Now I had hoped that in 1988 when I came to the NIH that perhaps over my professional lifetime that might change. Unfortunately it hasn't. But that has been a matter of necessity more than invention because as

I continue to practice, I know that I need to do something.

And often times what you try and do is you draw from what is off the shelf. Sometimes those things really do affect the core symptoms of the disease.

I would have been the last person to think that, say, the antidepressants would have effectively treated a panoply of disorders from depression to anxiety to OCD to generalized anxiety disorder, many things that we believed had different roots and may have different pathophysiological roots. But nonetheless seem to respond, at least in some way that is clinically relevant.

Some of the trends in psychiatric drug development that I've seen over the last ten years since I've been at the FDA is the number of applications for new chemical entities are down but the number of applications for supplemental indications or new marketing claims are up.

Since I've been at the FDA in the last ten years, I've seen all of the new atypical

antipsychotics come through, except for clozapine, which had already been approved prior to my starting at the agency. I actually was the primary reviewer for olanzapine many years ago -- well, about ten years ago now.

One of the things that I find and talk to people about when they're thinking about a career in psychiatry is most of what we treat we don't understand. The DSM-IV is a catalogue of disorders and not diseases. I know I'm preaching to the choir here but the distinction is that diseases are something that we believe we know something about. And disorders we don't make that assumption necessarily.

The beauty of the DSM-IV is it allows us to organize our thinking about a disorder as a symptom cluster. It doesn't claim to completely describe any disorder. The DSM changes with changing understanding and further observation. Generally doesn't comment on etiology since DSM-III; DSM-II and I did. There are few if any psychiatric symptoms that are unique to a single disorder. And probably more than anything, the

printed page rarely reflects a comprehensive image of the patient.

Now just an example of that is schizophrenia. And I'll be showing that page from the DSM in a moment. But when we approve drugs for the treatment of mental disorders, we base the approval on symptom relief within the context of the disorder.

And when I say that, we usually base that after the diagnosis has been codified either through the DSM or a structured interview using the DSM and then measured using the validated rating scale. Now improvement in function we also want to see, too, whether that is either measured or manifest.

And here's what the page from the DSM looks like when it describes schizophrenia. Now I can tell you that this does not at all reflect what a patient with schizophrenia looks like. And I remember as a medical student reading through the DSM and not really knowing what a delusion was until I actually saw one.

The same goes for autism. One really doesn't

understand what an autistic child looks like until one sees several, actually.

But I'd like to at least recognize the value of serendipity in drug development. Chlorpromazine, one of the first antipsychotics used in the schizophrenia population, was originally designed as an antihistamine, but when it was used in the schizophrenic population, there showed marked improvement in what was considered the core symptoms of the disease, hallucinations, delusions, grossly disorganized behavior for example.

This caused an improvement in functioning to the point that many of the state hospitals ended up releasing quite a few of their patients. There was a move in that direction.

As a matter of fact, some would say a move that went a little bit too far, leaving quite a few people homeless and under-treated. But that's another issue. One of the problems with the treatment, however, was that there was no clear evidence of the arrest of decline in social functioning.

Prior to the phenothiazines, barbiturates were used in the treatment of schizophrenia. They were used primarily to treat agitation and though descriptions are dated, it appears that the effects of the barbiturates on schizophrenic patients were similar to the nonspecific sedation seen when antipsychotics are used in autistic children or perhaps adults with Alzheimer's dementia.

Some of the similarities and differences between autism and schizophrenia drug development, both again are serious diseases. Both have pretty much unknown etiologies, though there are several good leads.

And in the end, the treatments are palliative and not curative, differences being that medical treatments improve core features with schizophrenia, not necessarily with autism, the preventions of acute episodes may slow progression with schizophrenia, though that I think is still debatable, and medical treatments improve patient functioning beyond merely decreasing agitation.

Now there are several regulatory pitfalls. And

these pitfalls apply to looking at developing drugs that are already marketed for the use in treating autism. We generally believe that if a drug is effective at treating some aspect, some fairly important aspect of the disease, then it should be approved to treat that disease.

The pitfall is that we don't want to create an artificial distinction where one does not exist merely to benefit a marketing strategy over another.

Some of those pitfalls we can see in individual rating scale items being celebrated when an entire rating scale is used to establish efficacy. Secondary efficacy claims that may be positive but not necessarily declared up front or that the use of multiple rating scales that really measure the same domain, or a subdiagnosis that hasn't necessarily been codified such as -- well, for example in the next slide you'll see the treatment of insomnia in the elderly with melatonin deficiency was an example that came to us.

This is what we refer to as pseudospecificity

-- the artificially focused identification of a general symptom as specific to a disorder. Insomnia is near and dear to my heart because I used to review that drug group. And we would get applications for things such as insomnia associated with gastroesophageal reflux disorder, insomnia associated with depression, insomnia associated with melatonin deficiency in the elderly.

And basically speaking, these were all either aspects that were part of the disease or that would disappear when the core disease was treated. These claims often come when there is a drug looking for a disease.

For example, in a post hoc analysis, it was found that in the use of one drug, it only seemed to be effective in treating the insomnia of the melatonin-deficient elderly.

However, as an agency, we're not prepared to recognize that as a disease. We don't necessarily want to take on all of the responsibilities of all the branches of the scientific government. We don't want to be the legislative, judicial, and

executive branches.

We suggested that this company bring these ideas that this is a specific disease entity out to meetings and groups like this -- or I should say analogous groups like this? So that it could be identified, discussed, and researched and then ? we like groups like you to come to us and tell us what to do, is the bottom line.

Another regulatory pitfall relates to safety. Often times we hear if a drug is already approved, then it is safe enough to use in other populations if it is effective. The pitfall is that acceptable risk to benefit ratio in one patient population does not necessarily equate to safe use in another.

Probably the best example of that lately is that one patient group may be susceptible to a drug-related adverse event that is not detected or is absent in another. That example is the increase in all causes of mortality that we have seen in an analysis of the studies of the treatment of agitation associated with dementia in the elderly but that we don't see in the non-elderly

schizophrenia population.

Just briefly, this meta-analysis showed that there were increases, of course, in all causes of mortality. That will be presented at the new clinical drug evaluation unit meetings in June in Boca Raton the early part of next month. And we hope to have something published on that and available publicly soon. In the meantime, we have issued a public health alert and have suggested labeling to manufacturers of these class of drugs.

Now this finding was not present in the non-elderly schizophrenia population and there really weren't enough elderly schizophrenics in the studies upon which the drug approval was based to really make a judgment if all causes of mortality had increased in the elderly schizophrenia population.

That leaves us with several questions for you all. First of all, does the autism community value the approval of already-marketed drugs for relief of isolated symptoms associated with autism?

In other words, is agitation associated with autism something that you want drugs approved for

that you already have access to? If that's true, what does the autism community want studied in addition to what they already know about these already-approved drugs being used off-label?

And agitation is just one example. I've also heard some information about the obsessive-compulsive symptoms that are being treated with some of the selective serotonin reuptake inhibitors. So the question, again, what more do you want to know, beyond whether or not it seems to work, that you already know?

And then finally, what does the autism community consider as valid target symptoms for drug approval? We don't want, as an agency, to carve out symptoms for the benefit of any one particular sponsor. And it's with groups like you that we count on to make that judgment. If you feel like it is something that you want studied, we, as an agency, feel like we have to listen to that.

And one final note on regulatory balance. Not too long ago, I was interviewed by the Psychiatric Times about some adverse events with an injectable

form of an atypical antipsychotic. And this is one of the things that I wanted to get across but it never made it into the article.

So if you'll indulge me for a moment, this is something that I've always tried to say. And this gets back to how we've changed.

Ten years ago, my move to the FDA was basically funded by the Prescription Drug User Fee Act. It made it so that new drugs could come to market faster in the United States.

Every new drug will likely have problems that were not observed in its initial development program. This is inevitable. And this very inevitability is too frequently ignored.

Fifteen years ago, the United States was one of the last major countries in the world to make a new drug available. Though United States citizens were not able to benefit from the positive aspects of newer drugs sooner than other countries, they were protected from problems that appeared in the countries where the drug was initially approved.

In August of 1962, the FDA reviewer Frances O. Kelsey found problems with thalidomide in the

offspring of non-U.S. patients. She was given the President's Award for distinguished federal civilian service by President John Kennedy. She was cited for resisting the sale of the drug thalidomide in the United States, thereby preventing the birth of thousands of deformed babies in the United States as happened in Germany, Great Britain, Canada, and numerous other countries in the late 1950s and early `60s. This was the culture of the FDA at the time.

The agency was later told that we were too slow in getting drugs to market. The agency was told that this was unacceptable. This was the AIDS crisis.

The Prescription Drug User Fee Act provided the legal mechanism for drugs to be reviewed and approved faster. This made it so the U.S. became the country that more often approved drugs first instead of last.

The downside, however, of being the first country where a new drug is approved is that its citizens are the population at risk for rare and yet unknown drug-related serious adverse events.

This will be true for whatever country is the first to approve a new drug. It is also true that the last country to approve a drug will have the benefit of everyone else's experience and the last to reap any potential benefit.

Thank you very much.

[Applause]

Dr. Insel: We have just a couple of minutes for questions or comments.

Lee?

Mr. Grossman: Yes, I appreciate these two talks in describing the difficulty that the FDA faces in approving products for marketable use.

I'm not really sure about where we are right now in terms of drugs for autism because I think there is still much-needed work to be done. But it seems as though there's various tests and labeling issues that could be addressed by the FDA in a relatively short order.

For example, a lot of our kids have gastrointestinal dysfunctions. And there is a series of tests as well as treatments that can be applied. But because of the autism diagnosis, many

families can't get reimbursed for these tests or for the subsequent medicines that they use afterwards. Can you comment on that?

Dr. Andreason: Well, so what you're saying is you feel like if these things ended up being approved, then they'd get funded better? You think?

Mr. Grossman: Not so much funded, it's just that right -- well, right now it is a reimbursement issue. And, again, I'm not sure -- well, that crosses into another agency.

But that agency won't even look at reimbursing for these tests or for these medications unless it is properly labeled by the FDA. And there are some, like for gastrointestinal disorders, and I think people at ATN can speak well to this, many of our kids do present with this and because of the diagnosis and the fact that they are being scoped or some treatments being applied to ameliorate some of their autistic symptoms and it's not labeled as such for treatment of autism, the families have to come out of pocket for this very, very expensive treatment.

Dr. Andreason: Any particular drug you are thinking of?

Dr. Carbone: I think I understand what Lee is getting at. But I think the issue is where the problem is. The FDA, if they're going to make an indication for a drug, then they need to be presented with the data that shows that the drug is an effective and a safe treatment for that indication.

So what you're really saying, really from a point of view of prioritization of the matrix, what needs to be looked at so that this information can be presented to the FDA? There have been some drugs licensed based on analysis of published data. I think that would happen for some of the bioterrorism drugs. And Prussian blue was an analysis done by CDER that permitted it from the literature.

But for the most part, what you're really talking about is presenting the information to the FDA so that they can make the approval on the claim. And then with that labeling, then the reimbursement might occur.

Dr. Andreason: Sometimes we've run into the situation where even approved drugs are not necessarily reimbursed. And a good example of that is buproprion for the treatment of smoking cessation. I don't know too many insurance companies that will reimburse that. Yet that's completely approved. And the data is very good especially in combination with the patch.

Dr. Insel: Last comment. And then we're going to break.

Mr. Fade: May I make a comment about this? I think you are right on. The problem, a big problem is problem definition as you pointed out in your prior slide when you asked what are the collection of or list of symptoms that comprise autism and that you would like us to look into ameliorating, right?

The problem we have today, which is ATN doesn't -- we're formed on the premise that we don't know. And because we haven't been able to establish on a factual basis the prevalence of these issues, then there is no guiding principle, there is no bona fide for reimbursement.

So, you know, sort of what we're doing is really about establishing -- you know is this a common enough symptom of autism? Is there enough prevalence of these health issues in autism for them to become part of that list?

But if you go back to the three questions you asked us at your close, I really think those were the things, you know, what is it that -- what is it we should be looking at, what collection of symptoms if there's like a top three or four of them that would define autism and, you know, how we should we direct our efforts as an agency to help look at drugs that can be responsive to that.

To me those are the interesting questions.

Dr. Insel: Yes. I don't think those are questions the FDA will ultimately be able to answer. My suspicion about this is that it goes back to the discussion we had this morning on the matrix.

The real key here is understanding the pathophysiology of this disorder so that you can begin to identify targets. What we don't have and why no pharmaceutical company is interested is

there are no targets for drug development to be able to take to the FDA. No one is really pushing that.

And without the appropriate molecular, cellular targets the way we have them for Parkinson's and Alzheimer's and other disorders that have really now become the engines for pharmaceutical development, we won't have this for autism until we get some of that hardcore science done.

At that point, then we can get the FDA to weigh in on what is a specific enough disorder for them to look at for approval. But right now there is very little interest in drug development except to find the -- we're hearing certain sort of side aspects but the not core aspects of this disorder.

Sorry to weigh in on this but I'm concerned about time. We do have a whole other session that is extremely important, a session for public comment. We want to begin that at 20 until four. So we have a ten-minute break.

Thanks very much to both Dr. Andreason and Dr. Mannheim.

[Whereupon, the foregoing matter went off the record at 3:30 p.m. and went back on the record at 3:40 p.m.]

Dr. Insel: A very important part of these meetings is the session for public comment. And I think what we'll do for this afternoon, we have many people who have signed up to make public comments.

If you could use the microphone at the other end of the table here, where there are several chairs with several mikes, we simply ask that you identify yourself and we all know you have much to say but there are also many of you who would like to say things. So we need to keep comments relatively brief so that everybody has an opportunity.

We actually do have a sign up so Ruth Sullivan. Perfect. Would you prefer to sit down? Because we have --

Ms. Sullivan: No, I'd prefer to stand up actually.

Dr. Insel: You've got it. Go right ahead.

Ms. Sullivan: All right. Here or at the

podium? All right.

Well, thank you for allowing me to make a few remarks.

Participant: Closer to the mike please.

Ms. Sullivan: Thank you for allowing me to have a few remarks, Dr. Insel.

All day long except for a few times, we were hearing about children and children and research and advocacy, looking at data, looking at all kinds of things, but not services.

About four years ago, I'm the provider of -- the agency is called Autism Services Center. We serve about 420 -- we serve 365 people with about 420 staff. Of that 365 people, about 100 have autism. I'm also the parent of an autistic child who is now 45 years old so I've been in this for a while.

I can tell you that when we first got started, if I had come to speak to an organization like this, a group like this, I would not have been allowed in the room because I was labeled a parent. So it is really rewarding to me to see that not only are parents invited but they are

honored to be here. So thanks. We really appreciate that you've come a long way. And I thank God I was able to see it.

So my son was 15 years old when Public Law 94-142 was passed. And he had been in school but only because his mother was pushy. And by the time he got out of school, I know that there was absolutely nothing for him when he got out so I started an organization called Autism Services Center.

It's now 25 years old. We have comprehensive services, comprehensive services for people with developmental disabilities, including those with autism.

I began to see that there were very few of us in the country doing comprehensive services, especially for adults because as adults get older, there is no entitlement. Once you get out of school, those of us who worked for mandatory education, we knew and I knew that when my son got out of school, there would be nothing for him unless I got it started. So we started Autism Services Center.

There are less than 30 of us, fewer than 30 of us in the country that focus specifically on autism. And even fewer of us who specifically focus on adults in residential settings. So that means that the adult, unless he has a home to live in, he doesn't have much choice about residential services in his community.

Most states still have institutions. About 14 states no longer have institutions. That's not bad but at least an institution was a place that the government would pay for residential services. Right now, the only funding there is for residential services is the waiver. There are no other deep pockets that pays for residential services.

And then the waiver is extremely limited. You have to have a slot. It has to be available. There are waiting lists in every state. And even parents who have been to court, when they win their case because they can't get services for adults with autism, even if they win the case, they cannot find oftentimes services for their adult with autism. Even with money, there are not services

that are appropriate.

So most adults are still living at home. Most adults are in inappropriate programs. Most staff in most of the places, they're not bad people. In fact, there are a lot of good people. But they do not have experience or training to work with adults and not supervision by the people who are just over them.

Most of the people who provide the direct care services are young kids. They are college kids in my town. We have a university -- Marshall University. And most of them are young, 18, 19, 20, 21 years old. And they're the ones taking care of some of the most difficult people there are to serve on the planet. And we're expecting them to do all kinds of very sophisticated kinds of things.

So in 2001, I called together a group of providers like us and sat them down at the San Diego Conference of the Autism Society of America. And we sat at a table this big saying do we have enough issues in common that we should have an organization. And it was unanimously yes.

So I was able to get a grant from the Administration on DD, Dr. Patricia Morrissey, and we pulled together a meeting and organized the National Association of Residential Providers for Adults with Autism. Residential providers. Now as I said, a lot of people are living at home.

But once that caretaker at home doesn't have the money or the energy or for whatever reason the caretaker cannot take that adult, they have to go someplace. So we decided we had enough issues that we would go after a Train-the-Trainer Project so that we could put trained staff in agencies who would like to serve adults with autism.

It's called Train-the-Trainer Project. It has gotten very good reception when we've presented it at national conferences. Parents are very excited about it.

We would have a three months intensive training for the people who manage the direct care staff. And when they go back to their sending agency, they would have three months under their belt of hands-on, face-to-face, not only how to work with adults with autism but how to be a good

manager. Also we give a managerial course because not everybody who is a good staff is necessarily a good manager.

It has had such a good reception and we are very encouraged. One mother told me at one of the sessions she says, "My 56-year-old autistic son is living with me. He has never been to school. I have terminal cancer. I am afraid to die. Please hurry."

Right now we're trying -- we set it out and then we went on -- we were only 25 agencies and we're barely making the bottom line all of us because you don't get very much reimbursement for what we do and the only deep pockets is the Medicaid, as I said, the Waiver Office.

So we asked the Autism Society of America to be sort of our cosponsor with us to try to get some funds to start a project of national significance. And we are together working. Lee Grossman is the CEO, Cathy Pratt is the Chairman of the Board of Directors, Anna Hundley is the President of NARPA. And I'm the Chair of the TTP Committee, the Train-the- Trainer Project.

We have a summary of it and, if you're interest, we can give you a very detailed plan for it. And what we would like to do is sort of get us on the road again to have some trained staff. This is a little bit where public schools were in 1975 when Public Law 94-142 was passed. There were very few special education people in 1975. There were even fewer who knew what to do in a classroom with a kid with autism.

So in 94-142 there was a lot of money put in for training for teachers. Right now that's not an issue any more. We have plenty of special education teachers in the public school system, some of whom have good autism experience and credentials.

And once you get to be an adult, there is no cadre of trained staff specifically for adults in residential settings. And we are proposing a project that would last six years. In six years, we would train 138 trainers who would go home and train other trainers. And each trainer, based on what the 25 agencies within our organization understand, each of the trainers would go home and

train ten direct care staff a month. So that at the end of six years, we'll have trained 138 trainers and each of those trainers would have trained ten a month. So that by the end of six years, we would have trained almost 50,000 direct care staff. And we would have that staff with over 7,000 clients.

So that's our project. It's a big one. I could go into detail. It would be a lot of fun to go into detail. We're excited about it. We've met with people who think it is very doable. It will cost some money, of course, and we're visiting the Hill tomorrow.

It is something that is truly a crisis. If we don't do something now, we'll have to start opening up institutions again or do what Hitler did, dig a big ditch. We're better than that. We can do a whole lot better than that.

Thank you.

Dr. Insel: Thank you.

[Applause]

Ms. Redwood: Hi, my name is Lyn Redwood. I'm speaking here today as a representative of the

Coalition of Safe Minds.

In 2000, founding members of our organization met with members of NIH, CDC, and FDA voicing concerns related to the fact that a decade of infants have been exposed to mercury far in excess of federal safety guidelines.

Our concerns arose from the fact that there was an extensive overlap of symptoms that were found to occur in both cases of autism and mercury poisoning. There was also a temporal association of the increasing rates of autism during this time period secondary to increasing the number of vaccines added to the early infant schedule.

And also something that I wanted to mention earlier that is often overlooked. The American Academy of Obstetricians and Gynecologists also recommended that all women with Rh-negative blood type receive a mandatory dose of Rho[D] immune globulin product at 28-weeks gestation. And at any time during the pregnancy when there would have been an invasive procedure or bleeding.

So there was a very large increase in terms of prenatal exposure to thimerosal as well which is

very often overlooked. And those could be very large. For myself, that was 130 micrograms. So just to add that in.

There was also at the same time reports that we were hearing that when children were tested, they had very high levels of mercury in their body. And they were reporting that these children were improving with nutritional supplementation and with chelation therapy. And some were improving to the point where they completely lost their diagnosis of autism.

So we decided to investigate these concerns. Safe Minds has sponsored over the last three years over 450,000 dollars specifically in thimerosal autism research. We're the largest funder of mercury-induced neurological research in this country.

And I would like to take just a moment to share with you some of our findings. We recently shared these with Dr. Ken Olden at NIEHS. And one of the questions he asked was if the interagency was looking at these issues to which Dr. Lawler, I think he's here today, said that they were not

aware of these. So I decided to come and just share a few of them with you.

You are probably aware of the study family histories of children with autism are consistent for autoimmune disorders. In an effort to investigate the role of genetics in autoimmunity, Dr. Horning exposed autoimmune disease-sensitive mice and control mice to vaccine levels of thimerosal modeling the childhood immunization schedule.

Autoimmune disease-sensitive mice showed greater growth delay, reduced locomotion, exaggerated response to novelty, and densely-packed hypochromic, and hippocampal neurons with alterated glutamate receptors and transporters.

Strains who were resistant to autoimmunity were not susceptible. And the behavioral pattern and neuropathological findings described in these mice suggest a strain-dependent ethyl mercury-based disruption of normal programs of neuronal development in synaptogenesis which was very similar to autism.

Another study that we funded was from

researchers at Northeastern University. And they documented that thimerosal at very low nanomolar concentrations like we heard today inhibited insulin-like growth factor and dopamine-stimulated methylation in human neuroblastoma cells. And it indicated its potential to disrupt normal growth factor control in myelination.

Levels of thimerosal exposure that produced these abnormalities were well below documented levels known to occur in infants after exposure to thimerosal-containing vaccines.

Methylation is critical for the development of sulfur-based thiols like glutathione. In addition, recent investigations have documented that thimerosal inhibited methionone synthase-dependent methylation in lymphoblast cells from same sex siblings discordant for autism. And that the extent of inhibition was far greater in cells than from those of autistic siblings.

This investigation provides a molecular explanation for how the increased use of vaccines and other products that contain thimerosal could increase the incidence of autism.

Dr. Jill James, who is a Professor of Pediatrics at the University of Arkansas for Medical Sciences, began analyzing plasma from autistic children and control children and discovered that the levels of several metabolites in the autistic samples were severely abnormal compared to controls.

She found that the autistic children had low levels of sulfur- based amino acids, methionone, and cycteine, which are essential precursors for the synthesis for glutathione, which is a major intracellular antioxidant that we heard Dr. Pessah speak of today.

Glutathione binds with mercury and carries it out of the body in the urine and feces. And without adequate levels of glutathione, autistic children cannot excrete mercury normally, which results in tissue accumulation, preferentially in the brain, kidney, and gut.

These findings indicate genetic influences and maturational factors as critical determinates of postnatal thimerosal sequella.

As I mentioned previously, Safe Minds also

approached NIH requesting for investigations into thimerosal. And as a result, NIEHS along with NIAID funded a primate study with Dr. Brubacher that you heard a little bit about earlier where infant monkeys were exposed to vaccine levels of either ethyl or methyl mercury.

And it was found in the study that ethyl mercury had a shorter half-life in the blood than methyl mercury. The fact that blood mercury levels resulting from exposure to ethyl mercury in comparison to methyl mercury are lower has been misinterpreted by some to indicate that ethyl mercury is less toxic than methyl mercury.

Unfortunately, blood is not the organ of toxicity. And blood levels do not accurately reflect tissue distribution or body burden. What has been overlooked in this investigation is the fact that there was a much higher proportion of inorganic mercury in the brains of thimerosal-exposed primates, up to 71 percent versus 10 percent for the methyl mercury group.

What makes these findings so hugely important is that inorganic mercury in the brain -- and this

is a question you asked earlier -- is the most toxic form in that it becomes trapped. And Dr. Brubacher in his earlier investigations found that inorganic mercury in the brains of adult primates was associated with microgliosis and neuroinflammation.

Just a few months ago, researchers from Johns Hopkins reported finding an active neuroinflammatory process in the brains of children with autism. This is the first time it has ever been looked at. And this included marked activation of microglia.

Now one would think that these investigations would be front page news. But the sad fact is that they are not. And to my knowledge, NIH has no plans to continue any additional investigations into Dr. Brubacher's findings even though they were called for in his article.

Safe Minds along with support from Autism Research Institute and the National Autism Association will further these critical lines of inquiry.

When I've looked at NIH research in the past,

it seems like the funding is going more towards genetic research. There is an effort to describe what autism is and to look for an elusive gene. But I don't really see a serious effort to look at the root cause of this devastating epidemic.

Parents of children with autism are becoming impatient with the slow progress of autism research. And Dr. Andreason, I don't think they want a drug to treat symptoms or a drug to mask the symptoms of autism. What the parents want is a cure for autism. And many of them report that they have found it.

As I mentioned earlier, parents are reporting dramatic improvement following the administration of supplements that augment methylation and support the production of glutathione. Why aren't these inexpensive and potentially beneficial therapies being investigated rigorously by NIH or FDA?

Why when children have been found to have excess body burdens of mercury when they were administered a chelating agent, why doesn't NIH have plans to try to replicate those studies?

These reports just seem to fall on deaf ears.

And I'm here today to ask that NIH make a dramatic change in the direction of autism research. Personally, I don't think autism is a mental health disorder. It is a physical disorder. And our children are very, very sick.

We're asking that you join Safe Minds in trying to expand this research. We feel as though we've laid a good foundation. And we want to see these studies replicated. We want to see them published in peer review journals. And we want to advance the science. And we'd like to partner with you to get this done immediately.

Thank you.

[Applause]

Dr. Insel: Thank you.

Mr. Shestack: Tom, could I just -- I think early today Dr. Swedo said that one of the things the Intramural Division was going to be considering was a chelation study. Was that something that you said? So we would just -- I would just urge you to, as you're designing that, go out into the community, particularly to the

people at Safe Minds, and get their input on it when it's being designed. Thank you.

Dr. Insel: It's often very difficult to get studies like that through the peer review system, which is an advantage of being able to do this intramurally.

Ms. Bono: Thank you, Jon. And there's also very many DAN doctors who have a lot of information on chelation right now. They're working with children.

I'm Laura Bono of the National Autism Association. Jo Pike, Scott Bono, Kathy Young, and Claire Bothwell will also be speaking for NAA today.

Thank you for giving us the opportunity to speak. It is our sincerest hope that you will consider our request.

As members of the IACC, you hold remarkable power where to direct the funding of autism research. NAA respectfully requests that you immediately change the paradigm of your funding perspective, change it from the majority of these children are born with a defect to the majority of

these children are born healthy then regress into poor health which leads to autistic behaviors. Ask yourself which would cause this poor health and what can be done to stop it now.

Parents have asked for years for NIH to study the children. We were convinced, and still are, that the ills in their bodies would lead to a cure. We became painfully aware that more and more of these children were being diagnosed and knew autism was at epidemic proportions.

We said to NIH at the time that we must study the children now. And that was over ten years ago. Ignoring that it is scientifically not plausible to have an autism epidemic, NIH has spent millions upon millions of taxpayer dollars looking for an elusive autism gene that does not and did not exist. The epidemic alone tells us that because we cannot have a genetic epidemic.

In every study that has ever been published with NIH funds claiming to have found a susceptibility gene has yet to be replicated. I beg you to stop wasting the taxpayer funds to look for genes now.

Our children need research that will lead to treatments and recovery. What we learn from the children now suffering with autism hopefully can allow us to prevent it from happening in other children. We can stop autism, but as a committee, you must look at the big picture.

As I stated previously, there cannot be a genetic epidemic. From all the science known to mankind, we are told that there must be an environmental trigger. So we must ask ourselves what would cause children all over the U.S. and recently in developing countries around the globe to regress at approximately the same time in their lives.

They eat different foods, have different lifestyles, sleep patterns, different air, water, nurturing, socioeconomic status, even different diapers, lotions, and other products. What one thing do these children have in common at approximately the same time in their lives that would cause them to develop symptoms that perilously resemble mercury poisoning.

When we overlay these critical questions with

what so many children's symptoms and what their health profiles are telling us through gastrointestinal, immune, toxicological, and molecular pathway testing, we begin to see a pattern emerge.

I ask you as scientists to begin connecting the dots and finally acknowledge the elephant in the room.

Ms. Pike: Okay. My name is Jo Pike. I'm the Executive Director of the National Autism Association. And I have a seven-year-old son who has autism.

We're going to lay it on the line. We believe that the elephant in the room is mercury. And the viruses that attack an immune system caused by mercury.

Our children are showing all the signs of it. Some parents are even removing it from the children's body in great quantities through chelation. And those children are getting better, some even losing their diagnosis.

As scientists, this cause and effect should inspire great enthusiasm to get to the bottom of

this phenomenon. We realize that the poisoning of a generation of children is not a popular theory. I don't even like thinking about it but I must if I'm ever going to get my son back and help the thousands of others struggling with mercury poisoning today.

Besides mercury, our children also have signs of viral overload. Many are showing measles in their guts. A number of studies now have been replicated proving these children have diseased colons showing colitis, lymphoid nodular hyperplasia, and decreased ability to digest their foods.

Additionally, the measles virus has been found in the spinal fluid of the children with an autism diagnosis, another frightening finding that cannot be ignored if we are to fully understand what has happened to these children.

Research is being conducted at Wake Forest Hospital which has confirmed the vaccine-strain measles virus from biopsies taken of autistic children. This was originally published in 2002 by Dr. John O'Leary and Dr. Andrew Wakefield.

It is amazing what you learn when you study the children. It is amazing what you could learn when you listen to the parents and the brave doctors who treat these children. The symptoms of our children's bodies told us that their immune, gastrointestinal, endocrine, and toxicological systems were being overwhelmed by toxins, viruses, and immunological dysfunction. Now research that has just scratched the surface is telling us the same thing.

We ask that you fund this type of research as soon as possible. NAA asks you today to make a major shift in funds now allocated for autism research. Stop spending millions on looking for autism genes or susceptibility genes. Even if we find the susceptibility gene or genes, what it will tell us is to avoid the environmental trigger that causes these genes to turn off or on in the first place.

It is literally putting the cart before the horse in spending money that could be spent on studies that will make a real difference for our children. We need to heavily fund new studies and

replication studies in four major areas: toxicological, gastrointestinal, environmental, and the molecular pathways that effect each.

Every single study needs to answer this question. Will this study lead to treatments and a cure for the children? In other words, NAA wants you to fund need-to-know studies versus nice-to-know studies. We want to know why our kids can't process heavy metals and fight certain viruses, have chronic inflammation, and dangerously high and low immune markers.

Please don't waste another taxpayer-funded study on yet another facial recognition study or how many self-stimulatory behaviors our children have. They are of no help whatsoever to the health of these children.

Thank you.

Ms. Young: I'm Kathy Young and I'm the President of the Virginia Chapter of the National Autism Association. NAA has provided a list of the growing body of research that we believe that IACC should concentrate on. We will not read it all here due to the time constraints but it will be

available in the testimony we are submitting for the record.

All of this research has been published in peer-reviewed respectable journals. We ask you to follow up on these studies. Try to replicate them for the real answers to the real problem. Ask yourself where can the truth lead and how can we use it to help cure the children?

Our children deserve better than what we have provided them so far. Although I'm very thankful for the 99 million dollars for autism funding because sadly I recall that only seven or eight short years ago the figure was five million. The truth of the matter is that autism funding should be ten times 99 million based on the enormity of the problem we are facing.

The new Confronting Autism Act of 2005 is another step in the right direction because it is requesting more funding recognizing this very important public health problem. However, it has a disturbing clause requesting that the funding for developmental neurobiology, genetics, and psychopharmacology commence immediately but

immunology, endocrinology, gastroenterology, and toxicology research not start until after July 1st, 2008.

We want to know why the wait of three years for this important research that will impact the lives of our children especially in light of recent research clearly pointing to an environmental trigger or triggers. NAA will be asking for the Confronting Autism Act of 2005 be amended to take this odd research stipulation out of the bill.

Members of the IACC, a huge task lies in front of you. Daunting as it may be, we believe you have a unique opportunity to cure over a million children suffering right now and stamp out autism altogether if you'll just follow the toxicological, gastrointestinal, immunological, and molecular pathway research to date and overlay the science with the children's profiles.

With this research, we believe you can create a biomedical therapeutic plan for parents to follow to help their children get better and perhaps cure them. Because the wonderful thing is,

parents are curing their autistic children every day with diet, chelation, and a host of other interventions aimed at fixing what ails their diseased child.

If parents can do it for some of the children, NIH can do it for all. It is really that simple.

NAA also asks that you allow NIEHS to assume an even greater position in this curative effort due to the inescapable fact that an epidemic of autism cannot be genetic and therefore is clearly caused by an environmental trigger.

What agency has more experience with this type of problem? We need them to lead us to the answers, treatments, and cure.

Thank you.

Mr. Bono: My name is Scott Bono. I'm from Durham, North Carolina.

All day today I've been going in and checking my son and anyone with an autistic child understands the state of hyper-vigilance that we as autistic parents live in. Well, the funny is I get this message on my phone and it's my alarm in my house going whoo-whoo- whoo. And here is my

son's tutor screaming at me, "Scott, you forgot to tell me the code to your house." So our lives are crazy.

What is really wacky though to me is to see the complete illogical perspective that we get as parents every day from educators -- our own family, our friends, our neighbors sometimes because we do have children who behave oddly. This is basically a disease or disorder -- a problem of behavior that is diagnosed simply on the basis of behavior.

With that in mind, we are asked by Institute of Medicine in May in their report to buy that excessive exposure to mercury would not lead to mercury poisoning. I want to thank each and every one of you here today from the bottom of my heart. I know your sons', your daughters' names before I know you guys. And I know the children's names before I know the parents.

I wouldn't wish this on any parent because I know the child of that parent would be suffering. My son is 16 and I don't want to have to think about an adult living center for him. But I also

don't want to not think about adult living centers for other people who are suffering with autism today.

Let's cure the thing. Let's have no protected ground or policy in this nation that we're willing to sacrifice a certain group of children for the betterment of all. We don't need that false choice. Let's make the thing safe. If it is this, if it is vaccines, let's fix it.

I don't want a dollar. I wake up tomorrow you give me money because my kid is injured, I wake up with the same problem the day after. I really want a cure. I think that's what we all want. That's why you're here.

Your devotion to this problem humbles me. If you don't have a child that is autistic, thank you. If you do have a child that is autistic, thank you for taking the time to be here. Thank you.

[Applause]

Dr. Carlson: Hello. My name is Jane Carlson and I'm here on behalf of the National Autism Center.

The National Autism Center is a new agency that's currently under development. It's being supported in its development by the May Institute, which this year is celebrating 50 years of service to people with autism.

The mission of the National Autism Center is to promote evidence- based practice for education and intervention. And we'll be working on developing a wide range of projects to guide families, practitioners, educators, and policymakers.

I wish I could have spoken after Dr. McPherson this morning because what I have to say really relates to what she was saying about practice guidelines and standards. One of our first projects at the National Autism Center is called the National Standards Project. And what we'll be working on producing is a manual of practice for educators and clinical behavioral practitioners who serve children with autism using a comprehensive consensual validation process.

One of the things that we've been hearing about today is a lot of medical research. And it

is always very interesting to me to come to conferences like this and hear about that. What we're focusing on is working on helping families who are affected and school districts who are trying to develop programs to support children make decisions about what is going to be effective practice with their children today.

The National Standards Project will build on the 2001 National Research Council report and its literature review. What we're planning on doing is convening a consensus conference this fall which will bring panelists from around the country to address this problem of standards.

Panelists who have currently agreed to participate in our project include Edward Carr from the State University of New York at Stony Brook, Glen Dunlap from the University of South Florida, Sandra Harris from Rutgers University, Lynn and Bob Koegel from the University of California at Santa Barbara, James Luiselli from the May Institute, Gail McGee from Emory University, Ray Romanczyk from the State University of New York at Binghamton, Ilene

Schwartz from the University of Washington, among many others.

Project advisors will direct the process and assist the panel in developing our procedure to go along with guidelines for evidence- based practices. We'll be advised by Carl Dunst from the Center of Evidence-Based Practice, Catherine Lord from the University of Michigan, and Dennis Russo from the May Institute.

The process will involve four stages. First is literature review. And we all know how great those are to do, right? Those of you who have done them. We'll be looking through all of the literature using computer enhanced search strategies and then we'll be delivering a final list of articles to be reviewed to panelists for inclusiveness.

During the next phase we'll be evaluating the literature that has been identified and what we'll be doing is holding a plenary session where the panelists will meet to review practices and code them based on the support of evidence. Some practices will be considered standards, others recommendations, and still others without basis in

research.

The entire process will be subject to peer review. We'll have representative experts from other disciplines who serve children with autism review the process and products at various phases.

Feedback will be provided to guide or redirect the group with the goal to ensure that the process and product are compatible with best practices in their disciplines.

The final stage is dissemination. Panelists will review draft summaries of their work and edit them to ensure accuracy and comprehensiveness.

The result will be a technical manual for wide distribution. The technical manual is the basis for further dissemination into user- friendly documents, peer-reviewed journal articles, implementation guidelines for education administrators, strategies for teachers, handbooks for parents, and guidelines for other disciplines who advise families and schools about educating children with autism.

Thanks for your time. And we're really looking forward to in the future updating you on how we're

doing with our project.

[Applause]

Dr. Insel: Thank you.

Audience Member: Excuse me. I didn't get the opportunity to sign up. Can I just make a one-and-a-half minute statement?

Dr. Insel: You've got it.

Ms. Moreno: I love this step. My name is Susan Moreno. I came here today from Crown Point, Indiana, which I'm sure you've never heard of. I've been a member of the Autism Society of America since 1976. My daughter was diagnosed in 1975.

She's now 33 years old. She speaks three languages fluently. When she was three, they said she'll live out her life in an institutional setting. She will not recognize you as her parents and her IQ is hopefully 70.

We got the benefit of the knowledge we gained at the ASA conferences and from many wonderful professionals.

Our mentor was Ruth Sullivan along the way. Our daughter had -- there were no manuals of like

people with autism at that time who could produce some speech. She didn't communicate well but she could use nouns. She knew the nouns for everything.

She now has a master’s degree from college. She types 60 words a minute. She has perfect spelling, punctuation, and grammar. In second grade, she told the librarian that the McMillan Children's Dictionary was bad because it didn't have the words perigee and apogee in it.

Beth cannot hold down a job. We are going to have to tell her when I go home that we're going to be moving her out of her apartment. She doesn't get SSI. She has her great grandfather's violin which is worth 1,500 dollars and she plays the piano. So she has this kind of pathetic keyboard. But anyway, possessions amount to over 2,000 dollars.

She's been saving her allowance since she was a baby, half of it religiously. So now she has the king-sized savings of 12,000 dollars. She can't have SSI. She can't have services. And when I die, she's probably not going to get into a wonderful

program like Ruth has started.

I have a 56-year-old -- pardon me, 59-year-old -- he's my age and I don't like to say that age -- very severely mentally retarded cousin who we rescued from an institution many years ago.

And I can remember the most exciting thing was when we got him into a group home was he kept saying -- Jimmy doesn't talk real clearly -- and he kept saying my woom, my woom. He wanted me to see that he could have pictures of his family on the wall and a stuffed animal. He couldn't have those in the dormitory setting because they disappeared immediately.

So I've kind of seen all ends of the spectrum. And I'm not here on my daughter's behalf or my cousin's behalf. I'm here as the listener of stories from 56 countries that we've had touch with over the years saying that if we don't get -- as Lee has said and Ruth has said -- keeping in mind constantly we need more appropriate programs.

I hear from the people around the country and around the world who aren't in services who are homeless. Many of them are in the prison system. I

cannot tell you how many letters we get from prison. Or we get letters and they say well right now I'm in a shelter. This is the address.

So we'll start sending them our newsletter and trying to have contact with them. Then they disappear again and we find they're living in a van or they've gone to the next homeless shelter. This is not a few people.

We are in contact with hundreds and hundreds of people like that. And sadly we're in contact with families whose young adults and middle-aged adults have committed suicide because there was no place for them in this world.

Please keep coming up with new ideas so that we have the programs we need. And help the good programs that are there.

My daughter did not become autistic. And I understand the very sad story of some of these wonderful people here today who have had children who have the childhood disintegrated disorder of autism. And that is horrendous. My daughter was screaming 12 hours a day from the day she was born on. And keening screaming.

So probably mercury or lead didn't do it. But if you think that I don't care whether or not it has happened to them, I do care because I have a lot of parents who have had that experience there, too.

I guess what I'm saying is keep an open mind. But as Mr. Grossman has tried to say many times here since he's been on this committee, please remember we have to have services for children and adults.

If we don't have the programs nothing else matters because they will all be gone from us and out of touch from us for those of us who don't fit perfectly into the system.

They're going to disintegrate into -- really, you're really better off in this country being a murderer than you are being an adult with autism who doesn't qualify for services. And I really mean that from the stories that I hear.

Thank you.

[Applause]

Dr. Insel: Thank you. We have about one more minute for public comment. Go ahead.

Ms. Polinsky: Just to add to what you said about group homes and services for adults, my son is living in a group home for three years now in a very successful situation. He's sort of high-functioning autistic but he -- well, anyway, the reason I'm here is because the agency he's living with is running such an incredible group home.

They train so beautifully I would recommend this agency as an example for how to train their staff, how to keep their staff, because that is one of the biggest issues across the nation. I'm from New York. My name is Bernice Polinsky, by the way.

We find that they're not paid well enough to keep the staff. They train them and they leave. And this agency keeps their staff. They rise within the agency. They want to stay with this agency.

And this is one of the things we would like to see all over. We'd like to be able to recommend that you check out this Yai Agency that is New York, Yai/National Center for Developmental Disabilities. And if anyone needs the telephone

number, please speak to me about it.

I cannot rave more about it. They are so incredible. The sensitivity and the in-house training is exceptional.

Dr. Insel: Very good, thank you. We have just a few minutes left for closing comments. And I wanted to just mention a couple of things by way of summing up. I think what we're hearing from public comment as well as through much of the day is the importance of continuing a focus on services. And I would like to encourage you to go back through the services roadmap which you have in your package.

Ann will be sending out a note in the next couple of days asking for your concurrence with this proposal or if non-concurring, we'd like to know what your concerns are so that we can communicate that back to the services group. We'll be looking to them for an update on this in November. And certainly we'll want to move this along quickly.

I know Lee has been very involved with this process but it is one that I think as you can tell

from public comment, people are really looking to us for some leadership on this particular part of the autism challenge.

The second piece has to do with the autism data sharing effort which you heard about this morning. We are eager to move that forward and we'll expect to communicate with you probably electronically about where that is going over the next few weeks or month or so. And we'll give you a much better sense at that point, I think, about what we will be able to accomplish.

The next meeting will be on November 17th and at that time, we should be able to give you a better accounting of where that effort is. Hopefully by then, it will be off the ground and running.

Also as I mentioned before, we'll be putting together this RFA for the next generation of centers. These are the Autism Centers for Excellence, ACE, and we'll be eager to have some discussion about that hopefully by November.

Before we close, other comments from anyone on the panel here? Jim, you've been quiet today.

Anything to add? No?

Dr. Cooper: Question on the date. You said 17th or 18th?

Dr. Insel: November 17th is our next meeting. It's a Thursday.

Okay. I want to thank all of the public participants. We really appreciated having you here. We appreciated your comments. We do hear what you're saying and we take your comments very seriously.

I also want to thank everyone on the committee as many of you who traveled from far to get here and appreciate your advice and wisdom.

See you in November.

[Whereupon, the above-entitled meeting was concluded at 4:26 p.m.]