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NATIONAL INSTITUTE OF MENTAL HEALTH

INTERAGENCY AUTISM COORDINATING COMMITTEE MEETING

FRIDAY, NOVEMBER 19, 2004

The committee convened at 9:04a.m. in Bethesda, MD at the National Institutes of Health, 31 Center Drive, Building 31, Conference 10. Dr. Thomas Insel, M.D., Chair presiding.

PARTICIPANTS:

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

ANN WAGNER, Ph.D., *Executive Secretary*, National Institute of Mental Health (NIMH)

KATHRYN CARBONE, M.D., Food and Drug Administration (FDA)

JOSE F. CORDERO, M.D., M.P.H., Centers for Disease Control and Prevention (CDC)

BARRY GORDON, M.D., Ph.D., Johns Hopkins University

LEE GROSSMAN, B.S., Autism Society of America

STORY LANDIS, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS)

PATRICIA MORRISSEY, Ph.D.

JON SHESTACK, Cure Autism Now

DENISE DOUGHERTY, Ph.D., Child Health and Quality Improvement, Agency for Health Care Research Quality (AHRQ)

PARTICIPANTS (continued):

MARY GANT, Ph.D., National Institute of Environmental Health Sciences (NIEHS)

JAMES HANSON, M.D., National Institute of Child Health and Human Development (NICHD)

DEBORAH HIRTZ, M.D., National Institute of Neurological Disorders and Stroke (NINDS)

GAIL HOULE, Ph.D., U.S. Department of Education (Ed)

ALICE KAU, Ph.D., National Institute of Child Health and Human Development (NICHD)

MERLE McPHERSON, M.D., Health Resources and Services Administration (HRSA)

STEVE MOLDIN, Ph.D., National Institute of Mental Health (NIMH)

MARGARET SCHAEFER, M.A., Administration on Children and Families (ACF)

SUSAN SWEDO, M.D., National Institute of Mental Health (NIMH)

BALDWIN WONG, National Institute on Deafness and Other Communication Disorders (NIDCD)

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PROCEEDINGS:

Dr. Insel: Good morning. Welcome to the semi-annual Interagency Autism Coordinating Committee meeting. We're delighted to have so many people here both at the table and around the outside of the room. As always, because there are some new faces and there are many people in the room who may not know who's at the table, I would like to just do a quick round of introductions. I'll start.

I'm Tom Insel, the Director of NIMH and designated as Chair of the Committee.

Dr. Swedo: I am Sue Swedo, the Associate Director for Child and Adolescent Research at the NIMH.

Dr. Cordero: Good morning. I'm Jose Cordero, Director of the National Center on Birth Defects and Developmental Disabilities at CDC.

Dr. Landis: Story Landis, Director of NINDS at NIH.

Dr. Hirtz: Deborah Hirtz, Program Director for Autism at NINDS.

Mr. Shestack: Jack Shestack from Cure Autism

Now, a public member of the IACC.

Dr. McPherson: Merle McPherson, Director of Services for Children with Special Health Care Needs in HRSA.

Mr. Grossman: Lee Grossman, Chair of the Board of the Autism Society of America and a parent of a child with autism.

Dr. Dougherty: Denise Dougherty, the Senior Advisor for Child Health and Quality Improvement at the Agency for Health Care Research Quality, U.S. Department of Health and Human Services.

Dr. Gordon: Barry Gordon, a behavioral neurologist at Johns Hopkins in Baltimore and the father of a 12-year-old with autism.

Dr. Wong: Buck Wong, NIDCD, Office of Science Policy.

Dr. Carbone: Kathy Carbone, Associate Director for Research, CBER, FDA, sitting in for Dr. Goodman, Center Director.

Dr. Gant: I'm Mary Gant with the National Institute of Environmental Health Sciences. I'm a Program Analyst and Congressional Liaison, and I follow the autism issue very closely from both an

interagency and a congressional perspective.

Dr. Houle: Gail Houle with the U.S. Department of Education, the Office of Special Education Programs.

Dr. Hanson: I'm Jim Hanson. I'm Acting Director of the Center for Developmental Biology and Perinatal Medicine at NICHD, and I'm standing in for Wayne Alexander who cannot be here today. Family and health problems have taken away his flexibility this week.

Dr. Kau: I am Alice Kau, Program Officer from NICHD.

Dr. Wagner: I'm Ann Wagner from NIMH, and I'm the Executive Secretary of this Committee.

Dr. Insel: Thank you. Very good. Well, welcome to everybody. I am going to move up here to just introduce this and to kick off today's series of presentations. What I thought I would do for starters is to just throw out some of the recent data that all of us have been intrigued by in looking at how this field is moving. I must say, having now done this for two years and going through -- what? -- I guess this is our fourth

meeting, it's really been an exciting period to see the research in autism begin to accelerate. A lot of this has happened just in the last few months.

So what I thought I would start with are providing you with some very quick overviews of some recent results that are not yet published, some of which may never be published but look to us like opportunities as this field begins to move forward at a much faster clip. We'll be hearing more in - depth from other people later in the day about some of these issues, but I thought I would take you through some of the sort of breaking news as a starter.

So we'll talk a bit about a couple of studies from genetics, a little bit about work that's going on, on environmental mechanisms that may be involved with the genesis of autism, and then very quickly a couple of recent findings from the neuroimaging world. These two actually are published and ones that you may already know about.

But let's start with the genetics story. This

is of particular interest. As all of you know, about 18 months ago, so mid-April of 2003, we had the final publication of the Human Genome Project with a full sequence, which I think everybody felt very enthusiastic about as being a kind of blueprint for human biology and potentially providing the road map of understanding human diseases.

It became clear very quickly, even before the publication of the final blueprint that, though this map would be very helpful in trying to understand what's different between humans and mice, it was probably not going to be very helpful in understanding why some children get autism and some don't. The reason for that is because what we had in April of 2003 was a consensus map. We had a map essentially of one person, and what we need for understanding human disease and the vulnerability to human disease is the map of variation.

What we began to understand very quickly is that actually the genome is all about variation, that none of us, unless we have an identical twin,

have the exact same sequence. We differ, on average, about one out of every thousand bases. Now the genome is 3 billion bases long, and that means that there is something like 3 million bases that distinguish each one of us from the person sitting next to us, so one out of every thousand.

This cartoon just gives you some sense of what that might look like if you were looking at a string of DNA, but it would be perhaps 10 million times longer than this, or I should say 3 billion bases in either direction. But if you could imagine single bases that were spread out here in which there was a difference, the problem was trying to understand how you match this variation to the development or the vulnerability to an illness.

The solution to that came about in a way that perhaps nobody would have expected in the beginning, but it was the recognition that actually, even though there are on average 3 million differences, they aren't entirely random. So if you match or if you map the genome on a series of people like is done here, what you begin

to see is that there are not just these single base changes, but that those come in certain blocks that are called haplotypes.

What that means is that you don't have to measure all 3 million. You may only have to measure some subset of those to be able to predict where all the variation is going to be. Indeed, that's the case. The haplotype map which is being done currently will be completed in the next few weeks. It should be done certainly by February. About 98 percent of it is done now. This is a project that involves at least four continents and many different research groups.

But what this will do at the end of the day, and the end of the day being February 2005, is it will allow us to do a map of human variation that doesn't require all 3 million bases being measured that are different, but only about 400,000. So it means that we can now make this a much more trackable problem. Four hundred thousand seems like a lot. Actually, it's a very doable kind of challenge at that point.

This changes the game entirely because now it

allows us not only to ask questions like, what are the differences in gene X between a hundred people with autism and their parents and a hundred people without autism and their parents? What it allows us to do is to look at the whole genome in what's called whole genome association.

We have been doing association studies one gene at a time. Now we can do them the whole genome at one time, and this entirely changes the game.

The first statistical test of this was just published last week in Nature Genetics showing that this is entirely feasible. Aravinda Chakravarti's group at Hopkins has really been on the forefront of this approach. The week before, in early November, the first scientific report, not yet published, but at least it was reported at the American Human Genetics meeting focusing on Crohn's Disease. Crohn's Disease, like autism, is a complex genetic disorder. There had been already from Eric Landers' group two genes identified as being high-risk genes, alleles that conferred risk for Crohn's.

This new study that was done with Perlegen was done by a private company of Crohn's with 500 trios showed not only that those two genes, indeed, were associated with risk for Crohn's, but it discovered 10 additional ones that we didn't know about through this whole genome association approach. All 10 of the new ones that were found had a much more powerful statistical association to then the two that we knew about.

So we're in a whole new era that's really just emerged in the last two or three weeks, and it will get much better. We have at NIMH just funded Dr. Chakravarti to begin to do this with autism. So he has some funding, although perhaps not enough, to begin this process using the AGRE sample and is off and running to try to get the first whole genome association on this disorder.

The other piece of this that's changed the turf a bit is the advent of these new DNA chips that will allow us to do a much more inexpensive and high - throughput process for doing genotyping. This also will greatly change the landscape.

If you think about it, the genome, when it was published, was the result of 12 years of work and about $12 billion in investment to get that first sequence. Certainly by February, we'll be at a point with both these chips and with the HapMap completed where we think we can do an individual for somewhere between $2,000 and $4,000 to do a whole genome sequence for any given individual, and the time course would be at this point about, depending on what system you use, probably about 96 people a week that could be sequenced in any given study at a single lab. So this is a tremendous and exciting change in our capacity to do genome sequencing, which may really have an impact on this disorder.

One other piece of genomic landscape that is changing that I thought I would share with you -- and, again, it is very preliminary -- is a paper that came out about six weeks ago in Science describing a new approach to looking at genomic variation. All of us have been very focused on these single nucleotide-based changes, single nucleotide polymorphisms.

A technique was developed by Michael Wigler and his associates at Cold Spring Harbor to digest DNA into small fragments, and then with a high throughput and relatively rapid approach, to sequence all of those fragments. When he did that, what he learned initially through studies of genes that were associated with breast cancer was that a lot of the variation in the human genome isn't based on single-point differences. There actually are these areas of the genome that seem to have rapid replication and produce what we call now copy number polymorphisms, or CNP. These are whole small chunks of the genome that become replicated. So you have multiple copies of certain small segments.

When Michael's group did this in this first study on just a group of 20 healthy controls, he found a surprising number of these -- in fact, there was something like 220 different copy number polymorphisms, 76 unique versions of this. The average length was about 460 kilobases and they spread out across the genome, some areas actually much denser than others. For reasons that are not

entirely clear, there are areas of chromosome 15 that are particularly dense this way. That's an area where we know there's been a tendency for imprinting and for a variety of other recombination effects.

What you have here is this kind of a map which is all 26 chromosomes that are laid out with the areas on the chromosome where he sees either one copy number polymorphism that shows up or sometimes multiple examples of this. This is really a little bit surprising for us because I think most of us had no sense that this was such a common form of variation, because in some ways it seems so massive when we've been so focused on individual bases and here you have whole small junks, like micro- satellites, that become redundant.

It turns out that the variation can go in either direction. You can either have an extra copy or you could have one less copy than most people have. So you have both gain-of-function and loss-of-function kinds of mutations.

Well, the obvious question was to do this,

then, in autism. Mike also decided to go after the AGRE sample because that was in the public domain, and he essentially did a very quick run through. The first run through was with 35 subjects. He's now up to 86. He began to look at whether there were more of these copy number polymorphisms in a group of autistic sample children compared to healthy controls.

These are, again, very preliminary data, but what he has found is that there were, indeed, a great number of CNPs of polymorphisms that he had not seen any time in controls. They were spread across much of the genome. Interestingly, many of them seemed to map onto areas where linkage had been previously reported, though these are very broad areas of linkage, and it wasn't a perfect match.

He's now extended this to about 86 children or 84 patients. In addition to finding copy number polymorphisms that were close to many of the candidate genes that have already been described, he has already fleshed out about 10 or 12 new, interesting potential candidates that will need

additional study.

So, again, I'm not sure that this is going to be the ultimate answer, but the opportunity to now look at both of these kinds of variation, both this whole genome association to pull out single nucleotide differences that may be important for identifying specific molecular lesions in genes and the Wigler approach here, which is called ROMA, which looks at a whole genome approach to looking at copy number polymorphisms, are likely to provide us some really interesting new candidates, and I think really move this field along much more quickly than we could have ever imagined even a year ago. All of this has happened, essentially, in the last four weeks.

A couple of comments about environmental studies because I think that, too, is moving much more quickly than we might have thought a year ago. Many of you know about this paper that was published two or three months back by Mattie Hornig and her colleagues at Columbia showing that, when you study Thimerosal in various mouse strains, giving Thimerosal once a day at ages

seven, nine, eleven, and thirteen, that actually you see very little in the way of behavioral or neurotoxic effects in most mouse strains.

But she studied one particular mouse strain called SJL. It's actually fairly well-known. It's an autoimmune strain that has a lot of physiological problems under the best of conditions, but these animals seem to be specifically and surprisingly sensitive to Thimerosal, even at low doses.

When they were looked at as adults, and that's what you see here, there were a number of what appeared to be toxic effects. They grew less. They showed loco motor retardation that was really very profound, and there were even some changes in the brain, which are a little difficult to understand.

The paper mentioned a number of these, but most of the techniques that were used were not quantitative, so it's a little hard to know exactly how big the changes would be. This is only one I pulled out that was focused on the campus where they did most of their analysis. It looks at the glutamate transporter, and it shows that in

one particular area -- this would be CA1, CA2 actually -- there seems to be a dropout of transporter in this particular area. You have to be a little concerned when you look at these kinds of data because (a) they're not quantitative -- this is immunocyte chemistry -- and (b) if you look, there's a lot of vacuolization here. So there's a problem with profusion of these mice.

But, still, it reminds us in a sort of rough way, anyway, that when we think about doing these kinds of studies of environmental influences on neuro development, we've got to focus on the genetic background at the same time, that not all mouse strains are going to show the same differences; not all humans are going to show the same differences.

This approach, which I think Mattie has pointed out is a potentially powerful one, allows us to go after the opportunity to look in different genetic backgrounds on how environmental challenges would play out.

This work is being followed up by investigators funded by HIEHS. Mary may want to

tell us more about that at some point, but there is a group that is going to be looking at this more carefully in terms of a better behavioral analysis and actually measuring ethyl mercury in the tissue, which wasn't done in this particular study.

Just one other very preliminary finding, one that's not yet published, but was mentioned at the Society for Neuroscience meeting and got many of us intrigued, from Pakco Rakic. He gave the presidential address this year at the Neuroscience meeting, which is attended by several thousand people. That lecture alone, the meeting itself I think had about 28,000 attendees this year.

Dr. Rakic is really one of the foremost developmental neurobiologists in the world. He has been pioneering the work on how cells migrate, how neurons migrate in neuro development and the paths upon which they migrate.

In some recent work he's become interested in whether there are environmental effects on these patterns of migration. One that he has pointed out that has surprised many of us are the effects of

ultrasound during pregnancy in mice. Again, I would say this is very preliminary. Its relationship to human disease is completely unclear, but I mention it here because this is likely to get a lot of attention over the next few months. I thought you should hear about it.

We're very concerned about this potential effect, and NINDS, since Story is here, may be able to tell us more about this because she's closer to the story, and is already funding Dr. Rakic to do some additional work in primates. We are looking at how this might be followed up to get a better handle on whether this is really or should be a concern or not, but we're all very curious about how this will play out.

I would just end up with a couple of recent reports on imaging findings which I think you should know about so we're all on the same page, again quite intriguing, although I would still say they are rather preliminary. One is a paper that was published just after our last meeting in May in the Annals of Neurology by Martha Herbert and her colleagues.

This was an attempt to take some rather older MRI studies in people with autism and to re-analyze them for white matter findings. This really tried to build on this observation that many people have had that, though autistic children have normal size brains when they're born, the brain and the head grow at a much faster rate than age-matched controls from about age one or two to about age five.

What Herbert and others have been thinking about is, is there a way to map where that's happening and how that's happening? So when they looked back at these scans, what they did was they did a particular segmentation analysis that allowed them to segregate out white matter and gray matter, and then to break out the different areas of white matter in terms of whether they were this sort of what they call radiate white matter that goes into the cortex, or deep-imbridging white matter, like the white matter that contributes to the corpus callosum. These are the long tracts that connect the hemispheres.

They simply asked the question, since we had

this sense that there was more white matter, more fiber in the autistic brain, is it in both sets of white matter or is it more segregated? It is quite interesting actually because the report found, when they did this kind of segmentation analysis -- here you see the radiate white matter and here the deep fiber bundles -- is that all the changes, which are quite significant in terms of amount, both in autistic kids and in the developmental language delay group are in the superficial radiate bundles here.

These are the tracts that go within hemisphere, so for these are for cortical-cortical connections and for intra-hemispheric connections. They actually come from a different part of the cortex. They come from layer three. They're not from the deep layers or layer four or layer five. That's the bridging zones.

There are actually very few changes in these deep imbridging zones, but just to give you some sense of the magnitude of this, it's actually quite profound. There's about a 35 percent increase in the superficial -- these radiate

bundles in the prefrontal area of the autistic brain, which is really a profound difference. We don't know exactly what that means. We don't know if that's a reflection of the loss of brain matter; we don't think so. We don't know how this gets driven. We're not sure how much of this is functional, but it's still, I think, an interesting observation that points us in a direction that needs to be followed.

We now have, of course, much better tools to do this. With diffusion tensor imaging, which is being funded through a couple of different mechanisms here, there will be a chance to follow up on some of this work.

One last story which I think is really very elegant is some work that was done with functional imaging, now not just looking at structure, but looking at how the brain is actually activated by different kinds of stimuli. This was a paper in Nature from a French group published late in the summer.

What they did is they compared autistic and control subjects on how the brain responds both to

non-speech sounds and to language itself. What you see in the top is how the control group is responding to language -- how the autistic group here is responding to language, the lack of activation in the superior temporal gyrus or in the Wernicke's area or any of those areas that we know are important for language comprehension and language processing.

Here is this profound difference between controls and the autistic group. You can see here there's almost no overlap, but the remarkable thing about this study is that, if you look at the scans that involve non-language processing -- so these were human sounds but non-linguistic sounds or non-social sounds at all -- there's absolutely no difference between the groups. So there is this really very profound and significant difference, but it's specific and unique to the way that language gets processed.

So that is just a quick rundown of some of the things that are happening that all of us are quite excited about. Almost every one of these stories now has someone around the table who is supporting

it and pushing it, and I just thought that this group ought to hear a lot of what is going on. Hopefully, when we meet next time, we can give you updates on a few of these things.

I'm going to stop there and see if there are any questions before we move into the rest of the discussion. Anything?

[No response]

Okay, we're going to move on to talk about the private/public partnerships. Steve Moldin is here. You're going to present the genetics RFA.

Dr. Moldin: Thanks very much. It's always a pleasure to be invited to speak before this group.

I want to talk with you about a new initiative that we are planning. So just a little background: The genetics of autism, what do we know? The mode event of transmission is unknown. We know that both genes and environment are important, but the relationship between genes, the underlying genes, and the disease phenotype is obscured. This is not a disease, for example, like Huntington's disease where, if we know a particular locus, we can make a 100 percent prediction about who's going to be

affected. It is an obscure relationship. There are some individuals with increased liability or partial liability and there's no disease expression.

Then, lastly, we also know that there are multiple genes that are likely involved, "multiple" meaning more than one, each of small relative effect, which makes them very hard to be identified.

Then, lastly, because of this problem, which is really a statistical power issue, I think it is very clear that we need very large datasets. When genetic studies of autism were started maybe a dozen years or so ago there was a sense that you might be able to study 50 families, 100 families, because of some previous studies that looked at the magnitude of genetic effects. Now it has become clear that we will probably need thousands of families to be able to identify these genetic effects.

What we have been doing since the last time we talked about this, since the last time this group met, is basically two sets of activities I want to

discuss. One we did in 2004 to enhance sharing of resources for genetic studies, and then an activity, an exciting new initiative we're planning for 2005 to actually identify specific autism susceptibility genes.

So in 2004, we wanted to move to accelerate the sharing of genetic materials, clinical data, genotyping information, and even DNA samples in our STAART Center projects. So the idea was to send to our repository data and blood samples. The NIMH repository, the NIMH Center for Genetic Studies is a resource akin to AGRE that has as its mission the distribution to as broad a representation of researchers as possible clinical data and DNA samples for genetic analyses nationally and internationally.

So we wanted to kind of facilitate the process that all these subjects being studied in STAART Centers that were suitable for genetic studies, the data and DNA samples become part of a public repository of information available to all researchers around the world to study autism.

The subjects that we targeted from which

sharing to occur in the projects were children and their relatives in STAART projects that were studying families, also children that were enrolled in a clinical trial and their parents. That configuration of individuals, an affected individual and the two parents of that person, are a study design useful in genetic analysis for association studies.

Then, lastly, affected children, children with autism who are unrelated in other STAART Center projects because those children, even without the parents being studies, those children are cases for case control association studies where another control group is found, not the parents, but other controls are used to look for associations with specific genes.

So this is a rich amount, a very large amount of subjects being studied in STAART Center projects. So what we did is provide supplements, three- quarters of a million dollars over four years, to be used for the consenting of subjects and drawing of blood and standardizing of phenotyping on those individuals in the previous

slide. NIMH supported this, and we funded five of the STAART Centers to do this: the University of North Carolina, UCLA, Boston University, Yale, and Mt. Sinai.

So, based on those efforts, this diagram shows right now in our repository, the NIMH Center for Genetic Studies, we have 400-plus families and 300- and-some-83 trios, and of unrelated individuals, about 200-so. So these three categories represent the three kinds of study designs most useful in genetic analysis: families of individuals, which could be multiple generations, not typically but could be, and relatives outside the nuclear family, cousins, et cetera; trios which are an affected individual and the two parents, and these are just affected individuals which can be used with a control sample for association analysis. So those are the three kinds of studies to use in genetic analysis.

So our existing data is by the red boxes. If we have funded, there was a peer review grant funded that supports efforts by colleagues at UCLA that are adding data to the AGRE dataset and also

to our dataset. This is the anticipated yield, and we're making strong progress on reaching these goals.

The supplement program is an activity that I described to you the last time we met, that we went back to investigators in the field who had collected data years ago to help transition that data to our repository to make a larger public access resource. Then, now, what I just described to you shows the additional yield, so about 240-some families, 435 trios, affected individuals and their two parents, and about another 2,000 unrelated affected individuals.

So by the time we finish with this, which will be probably two years from now, we expect to have in our repository alone about 1600 families, 1600 trios, and probably over 2,000 unrelated individuals for association analysis. So these are actually getting to be quite large datasets in the public domain anybody can access, any researchers can access.

Now the field has been moving very rapidly, and part of that has been to follow some of the

very exciting research develops that are really happening, that Dr. Insel described, that are really happening at a breath-taking speed in human genetics. So studies in autism have identified numerous candidate genes and genomic regions of interest, and now there are two very large datasets that are in the public domain for access by all investigators, the one maintained at NIMH and then the AGRE dataset.

Then, lastly, I think that the National Alliance of Autism Research, these efforts are really shepherded by Dr. Andy Shih, who has assembled a very large-scale collaboration of investigators, most of the investigators, almost all the investigators worldwide studying autism, to have a collection of 1300 families with probably over 3,000 affected individuals. They are starting to do a large genome scan in the search for genes, candidate genes, and genomic regions of interest.

I will mention that there is overlap between all three of these. So there are families in common in all three of these kinds of activities.

But, any way you look at it, I mean, having thousands of affected individuals and over a thousand families provides the field with a heretofore unrealized opportunity to do genetic studies.

This slide, I just wanted to kind of give you a sense of some of the findings that are happening in the field: whole genome linkage; studies have identified several regions; some people are now starting to do expression profiling, exciting new molecular methods by Wigler and others to look for variation across the genome; functional candidates, WIN2 and AREG 3 and 4.

Then, of course, we have the relationship at some level, some level of etiology or pathophysiology between autism and other diseases that share similar phenotypic characteristics, like Fragile X and Rett Syndrome, tuberous sclerosis, in which genetic factors have been identified. So this is starting to become a very exciting landscape, but the issue is, how much of these results, how many of these are real? Where are the real genes here? Which ones are the false

positives and which ones are real?

This is the motivation that has led us to now propose this new initiative. We're going to fund a new set of studies with a research activity, that the goal of it is really ambitiously to determine across this landscape, which are the real genes? Which are the actual real functional variants that influence susceptibility to autism?

Given that and given the now heretofore unavailable availability of large-scale resources and large-scale collaborations, this is really a very exciting time to actually identify precisely autism susceptibility genes. So, molecular genetic studies in pre-existing samples will be a focus of this activity, not collection of new data because we have a lot of data now, a lot of it in the public domain. We want to focus on the molecular genetic studies to find genes, fine map them, and then take the field to the next step, identify functional variants, actual variation within genes that cause susceptibility, and to understand how that causes susceptibility, and then positional cloning studies, and then, ultimately, broad

sharing of all these results with the scientific community.

The effort we're going to do now has an unprecedented support for genetic studies, and for complex disorders, and certainly in autism. We have a commitment of over $4 million per year, a total cost of over $21 million. This represents just an amazing public/private partnership between five -- it will represent five NIH institutes: NIMH, NINDS, NICHD, NIDCD, and NIEHS, the Canadian Institutes of Health Research; INMHA, which is -- I'm in a block on what that means, but it's the Institute for Mental Health in Adolescence, and IHDCYH; IG is the Institute of Genetics; I can remember that one [laughter], but it's three institutes of the Canadian government; the Health Research Board of Ireland; Southwest Autism Research and Resource Center; Cure Autism Now, and the National Alliance for Autism Research.

I want to say, I want to just give really credit to Dr. Andy Shih and NAAR because much of this work to kind of assemble and to stimulate the interest across countries in furthering autism

genetic studies lies with him.

So the way we're going to implement this is the request for applications, the RFA mechanism we use, which is a solicitation to the field for studies, and I'm only going to talk about it in a very general way because, until we publish this, we really can't go into specifics, but I can give you a general sense of what we will be interested in or what will be included in successful applications: high-throughput genotyping, state-of-the-art statistical modeling, association analysis and linkage disequilibrium mapping, positional cloning studies, possibly epigenetics, looking at non- traditional kinds of genetic mechanisms that might be involved in autism, and functional studies in experimental systems.

The scientific value of this: really to accelerate gene identification, which is going to give us insights into what causes autism, and then, finally, that's to jumpstart drug discovery. So I can't tell you how excited we all are at the prospect of bringing together three countries and private foundations together in one effort to do

what 10 years ago would be considered impossible or very grandiose or just not doable in our lifetimes; namely, to identify specific genes, specific variants that are involved with causing autism. I really feel like, if there are genes for autism, and myself and many people feel that there really are absolutely genes for autism; this effort is going to nail down which ones are those.

So that's all I wanted to say. Again, I want to just thank all of the partners because I stand on presenting this, but this work is really on the shoulders of others; namely, CAN which started the AGRE repository with the notion of creating large-scale genetic studies that were in the public domain for all investigators to access, a very important step in this process, and then the work of Andy Shih and NAAR to really bring together a very large group of geneticists, molecular geneticists, clinicians, neurobiologists to form a consortium to study the molecular genetic basis of autism.

We stand on the cusp, I think, of very exciting developments. Thank you very much.

[Applause]

Dr. Insel: Thank you, Steve. I think, rather than take questions now we'll go ahead and hear the next presentation. Then there will be a discussion with both Andy Shih and Jon Shestack, and we can take questions at that point.

I want to introduce next Dr. Lonnie Zwaigenbaum, who is a pediatrician from McMaster University. Lonnie has been actively involved both in genetics research in autism and for the last several years he's been working on studies with Susan Bryson in Canada of the younger sibs of children with autism.

He has had support from both NAAR and from NICHD to bring together several groups working on what we now call affectionately "the baby sibs study," and that's what he is going to describe today is this collaborative effort.

While the slides are coming up, just to put all of this in context, this is all connected to the autism matrix which we talked about a year ago at this meeting and again at the last meeting. One of the things to remember from the matrix was that

from the very outset Congress had challenged us not only to work as federal agencies to make some important things happen, but to work with the community and with public/private partnerships to realize some of these goals. So the point of these presentations this morning is actually to describe how some of those things are playing out.

Lonnie, thanks for joining us.

Dr. Zwaigenbaum: Thank you and good morning. Thanks very much to the IACC for giving me the opportunity to present to you today. I'm the Chair of a group of investigators and research groups following really a unique group of high-risk infants, younger siblings of children with autism. This is a general approach that has been taken with other conditions such as schizophrenia, working with relatives in order to identify early signs and genetically-transmitted impairments.

Autism really is a unique group and uniquely suited for this general approach, given that it's an early diagnosis. So that one can work with infants and then confirm diagnoses as early as two or three and really be able to sort out the

differences between high-risk infants who develop the condition and high-risk infants who don't.

This talk very much continues along the theme of private/public partnership, and we owe a great deal of debt to both the National Alliance for Autism Research as well as NIH, particularly NICHD and NIMH. This is also very much an international collaboration with research groups across the U.S. and Canada as well as support for our group from the Canadian Institute of Health Research, who brought us all those interesting acronyms which we heard about earlier.

As you see, the groups that are represented in this consortium include many of the groups investigating autism in the U.S. A number of the STAART and CPEA Centers are represented as well as our Canadian group. I think our starting point is the current data on early signs of autism. It is clear that we have learned a lot from the retrospective experiences of parents as well as analysis of home videotape studies. Really this is very rich data that's guided the early identification efforts in the public domain.

Looking at studies of retrospective parent reports, if one asks parents, upwards of 50 percent recall that there were differences even in the first year of life. Interestingly, what parents typically recall early on doesn't necessarily map onto the DSM4, but most typically it represents one of two extremes, either that the infants are very irritable and difficult to console and very distressed by a variety of experiences or almost the complete opposite, that people describe them as the perfect babies who never cry. For many families, it's a combination of the two where there are certain things that really upset the infants and yet there are many times it seems the infant is just quite content to be on their own.

There are certainly many other signs that parents recall, including signs more characteristic of our view of autism, including poor eye contact, lack of social interaction, and so on. You can imagine that for many families, as has been our experience working with the sib families, that it is after having a typically-

developing infant that the parent is struck, you know, the infant who is smiling and engaging and drawing you in; the parent reflecting back on how different the early experience is compared to their older child.

There are many studies looking at analyses of home videos which have given us a lot of insights about looking at early signs. One of the most important features to come out of early home videos is children's propensity to orient to human faces, a basic deficit in which may really sort of impact on early experience or early social experience.

There is also a very small number of isolated case reports, most recently from Ami Klin and Fred Volkmar and the Yale group, describing a young child who came to attention at 15 months and who was followed, and the early evolution of autism was described.

But, of course, there are a number of limitations in this general approach to identifying early signs. Retrospective reports ultimately will be colored by the later experience

of diagnosis, and the reliability of the description of early signs is going to be in some ways related to the degree to which parents sort of viewed the early signs as being significant at the time, and so signs that may be characteristic of diagnosis such as poor eye contact or lack of smiling may be most commonly identified, but other signs that don't map as neatly onto DSM4 may be less likely to be described.

Home movies and videotapes are a lovely living record of what children are like before diagnosis, but, of course, these home movies weren't taken with the intent of describing the full range of social impairment, and there's certainly a lot of variation in quality and length and context, which makes it somewhat difficult to integrate and combine the data.

And then case reports are incredibly insightful. Some of these, at least one case report actually followed a child who had come to attention at one month of age. But, almost by definition, case reports are unlikely to be representative. It may just represent the most

severe or kind of characteristic cases.

There are a number of advantages of approaching this using a prospective design, not the least of which is just the opportunity to apply a standardized approach, to look at early signs in a more systematic and comprehensive fashion, and to actually have the opportunity to test the specific hypotheses around mechanisms.

The other, I think, very important issue is the opportunity to assess predictors and outcomes in an independent way, where the assessment of early signs and the assessment of diagnosis is independent and we're not worried about sort of the biases of sort of the inherent association.

I think the other sort of not-as-obvious advantage is the opportunity to describe early signs in a broader sample. Until recently, and certainly thanks to the efforts of people working in early identification, we're seeing more and more children at the age of 18 months and two years, but until recently that was certainly not the case and the children who were coming to attention at the age of two tended to be children

who were the most handicapped, who had the most severe symptoms, and the description of their early signs is not necessarily going to allow us to identify the full spectrum of children.

So the mission of our consortium is really broadly to work collaboratively in our investigation of the early development of autism spectrum disorders in high-risk infants, and that this is work aimed at both improving early detection as well as allowing us to understand basic mechanisms by studying very young children as the early signs of autism are emerging.

Our collaboration includes specific projects, which takes advantage of the fact that we share ideas and share methodology involving common measures as well as pooled sample, sort of analogous to the approach in genetics, to improve power and also sort of overall efficacy of our efforts.

Just as important is the exchange of ideas and combined efforts towards addressing the methodological challenges in sibling research as well as the considerable clinical and ethical

challenges in working with a group of high-risk infants in whom early signs of autism are being detected.

I will talk a little bit about sort of the various projects and activities of this consortium, and then as an illustration of the kind of information and data that can be generated from these projects, I'll talk a little bit about our experience in the Canadian sibling research group.

Our first collaborative project is a study of head circumference in these high-risk infants, but with the idea of building on existing data to evaluate early patterns of head growth in a prospective way as possible early markers of autism, and specifically to look at whether the combination of early behavioral signs and brain growth patterns may improve the sensitivity of early detection approaches.

Clearly, the opportunity to identify these children early on and identify a biological marker such as increased head growth allows us to link to specific neuroimaging research and genetic

research, again to look at sort of the underlying mechanisms of this phenomenon.

Other specific projects that are under development: It covers sort of the wide range of potential activities of such a group. One is to pool our efforts in looking at early predictors. You can imagine that we have a number of specific research groups, each of which has their own unique and original approaches to looking at early signs. What we would like to do is sort of take out what's most common and perhaps most essential from these various protocols and really pool our efforts and expertise to identify the early markers of autism in the first six to twelve months.

Our initial experience suggests that there really is a lot to identify prospectively at 12 months, but at 6 months, although there's a qualitative sense that children who later are diagnosed with autism do have some subtle differences, our ability to differentiate children at that early age is much different than it is at 12 months. Whether that reflects a true biological

phenomenon or whether that is an issue of measurement I think still needs to be kind of better sorted out.

The ability for us to pool our efforts, to look at our early videos of our assessments, and distill some of the markers that perhaps we're not measuring systematically will give us an opportunity to look earlier in the first year.

Another subproject is an early diagnosis project. One of the clinical challenges of working with really young children is the fact that DSM4 was developed in a group of children who would be referred for assessment for autism, so really didn't include children who were younger than the age of two or two and a half.

Even the best diagnostic tools that we have operationalize DSM4 criteria, but for children who have developmental levels of at least 15 to 18 months. If we are going to sort of push the boundaries and have an opportunity to both identify and truly diagnose children before the second year and even before 18 months, we need to agree on a standardized set of diagnostic

criteria. But in order to do this, we need to have prospective research that allows us to sort of test our ideas about diagnostic criteria and ensure that they are stable.

Finally, despite sort of all the epidemiologic research and genetic research, there's actually relatively little that we know about how the characteristics of the older child in the family predict risks to later-born children. By assessing the older children in the family who are already diagnosed in more detail, we can look at both the familial traits, the similarities between the younger sibs and the older diagnosed sibs as well as characteristics of the older sibs that may actually impact on risk, even basic questions such as whether adaptive function or intellectual level in the older sib influences recurrence risk.

Other activities of the consortium include, as I mentioned, sort of addressing methodological issues. As a group, we have recently submitted a paper for review addressing the various methodological challenges.

We've also developed working groups aimed at

developing better approaches and better standards for communication of early clinical feedback as well as discussing the importance of early intervention for infants with early markers of ASD. This is an essential ethical dilemma that, as we identify children earlier and earlier, we come into uncharted territory in terms of autism-specific intervention, and we need to be developing these processes in parallel, both early identification as well as intervention.

With the support of NICHD and NAAR, we have been meeting annually, and our next planned meeting is early 2005.

So, briefly, I'll mention our initial experience among the Canadian group. At this point we have worked with a group of 176 families who have a child with an autism spectrum disorder as well as an infant sibling. Out of that group, we have followed 90 of these children to the age of two years, 11 of which have been diagnosed with an autism spectrum disorder and meet sort of full autistic disorder criteria on the Autism Diagnostic Observation Scale. Notably, none of the

controls have received a diagnosis at the age of two.

Just to describe what we are seeing, as I mentioned, there seems to be a qualitative difference and a change from the age of six months to 12 months. If you saw these six-month-olds in your home or in your clinic, you wouldn't necessarily be immediately struck that they are at increased risk of autism. They have reasonably good eye contact, social smiling, and appropriate range of social interests and affect.

What you might be left is with a sense that these children are somewhat quiet. They are not quite as interactive or perhaps don't initiate as much with other people. Notably, these children lack postural stability and show some subtle decreases in tone. Although there isn't sort of a clear developmental delay in terms of early milestones, there is a qualitative difference in tone and posture.

In contrast, as children go from the age of six months to 12 months, there are actually a number of specific behavioral markers that

measured prospectively really do differentiate the siblings who go on to a diagnosis of autism from those siblings who are typically developing. These are listed here: Basic deficits in visual attention, including visual tracking. You know, I was commenting to Marshalyn earlier that, although our focus has been on social babbling in terms of early speech development, we have been very struck by how quiet these children are, you know, how much they actually lack vocalization entirely. In a moment I will actually demonstrate this in a video clip.

Certainly decreased social behaviors, particularly in response to peek-a-boo; lack of basic imitation skills, and extremes of reactivity. Again, as parents describe, either sort of a complete lack of reactivity or extreme catastrophic reactions to sort of very minor stimuli.

Surprisingly, we're starting to see some atypical repetitive behaviors even as early as 12 months. Notably, these children have as a group some developmental delays, although there is

considerable overlap between the autism group and the siblings who don't go on to develop a diagnosis. So that you have some children in the autism group who are delayed but some children who have achieved sort of typical developmental milestones.

What I will do now is illustrate our behavioral assessment, and just as a contrast, to show you one little girl who was doing well and at the age of three continues to be developmentally typical and no specific diagnosis, and then another child who there were clear concerns at the age of 12 months who has been diagnosed with autism, initially at the age of 24 months, and now certainly the diagnosis is stable in follow-up at two and a half.

[Video]

Probability to shift and disengage from one object to another and you can't help but smile when you see these beautiful typically-developing children. You can imagine that the experience for the majority of families participating in this project has been that of very much of reassurance,

you know, having a child who is typically developing and achieving these kinds of milestones and then, in contrast, another little girl who clearly has some differences compared to the first.

[Video]

She does respond to her name, really emphasizing that no one of these signs if pathoneumonic for autism. Just the differences in or that lack of vocalization and facial expression. Okay, just to briefly summarize, we have a lot of very rich data that encourages us that autism can be identified early in life, and very much supporting early identification and detection efforts. We feel that prospective studies of high-risk infants may actually sort of round out our understanding of their early emergence and development of autism and may allow us to test some specific hypothesis about basic mechanisms, and that this is a consortium that's very much a collaboration of public and private initiatives, particularly the National Alliance for Autism Research and NIH through NICHD and

NIMH. We certainly thank them for all their support.

Thank you.

[Applause]

Dr. Insel: Thank you very much. We are scheduled to have comments from both Jon Shestack and Andy Shih, but this can be as formal or as informal as you like. Andy, would you like to come to the table? Jon, you're listed first.

Mr. Shestack: Really?

Dr. Insel: I know you're not at a loss for words.

Mr. Shestack: Well, okay. I didn't know exactly what I was supposed to be commenting on, but I would want to ask a couple of questions maybe of you and point a couple of things out.

The stuff that you updated us on is all very promising and it's interesting and it's exciting research, but I just want to be clear that it does seem to me that, since the Autism Summit, for instance, or since the last meeting that this group had, which was I guess in May, as far as I can tell, although many individual scientists are

which there are shared priorities, in which our processes are compatible, to at least temporarily move the science forward in a fairly aggressive fashion.

I think it's fair to say that all of us involved in the process probably recognize there are ways in which we can improve our relationship and collaboration and the collaborative process in general, and I very much look forward to working with the NIH in developing these additional solutions to make our process much more efficient.

But I think at the end of the day what we all need to remember is that, even in a crunch time that this is, and even in an environment where we all want more money to be made available to do research, if you look at that SIC consortium, if you look at that genetics research consortium, or more specifically the new authors of gene discovery RFA, what is really happening is that by the advocacy community taking a lead, much as Jon and Ken have done with AGRE in taking that first visionary step in terms of providing resources to the geneticist community and urging them to work

together, I think we have really built upon that first step in a significant way, so that with this RFA, not only is the voluntary sector contributing resources, but we're also getting tens of millions of dollars from the government funding agencies as well. I do see that as an accomplishment for us all as a community.

I guess I just want to thank the parents who have the vision and the perseverance to push through their vision, and I also want to thank, obviously, the NIH and other government agencies, specifically ex-Minister of Health Martin and the current Minister of Health Mary Harney of Ireland, Dr. Emick Cureo of SHRS, the Pacific Institute of Neuroscience, for really sharing that vision and be willing to explore new avenues to support authors and research under less-than-favorable conditions.

Thank you.

Dr. Insel: Thank you to both of you. Let's take just five minutes for discussion and then we'll move on. I'm sorry we don't have more time, but there's an awful lot to talk about. So let's

open this up for responses.

Dr. Swedo: I would like to respond to a point raised by Jonathon, particularly in regards to the data sharing. At the last meeting we had promised to be working on this and trying to find a more effective system that would really respond to the masses of data that would be accumulated between the CPEA STAARTs, the CDC centers, and NIH. I believe that we are making excellent progress on that.

In a meeting just yesterday with BRN and the CIT from NIH, we have a firm commitment for the Bioinformatics Research Network to provide us with the infrastructure needed to set up this network as well as the NIH CIT has agreed to serve as data coordinating center.

Now the money and logistics of this have to be worked out, but with those two commitments in hand we are ready to begin combining datasets. The nice thing about is that the BRN network was actually established with its first test beds used for neuroimaging both more for metric and functional neuroimaging. So, that capacity has already been

established in adult studies. That can be combined. They have experience in genetic data analysis as well as phenotypic and clinical. So I think it is very exciting and really meets the needs that we have all been worrying about for a while.

How that will fit in with other things is still being worked out, but I promise you we will have it done by the next meeting.

Mr. Shestack: What is CIT?

Dr. Swedo: Computer Information Technology.

Mr. Shestack: That NIH office?

Dr. Swedo: NIH office and they are actually separate from the National Library of Medicine, but what they envision is an archive similar to that being established in NLM for published papers and data.

Mr. Shestack: Well, that would be great, but I would like to afterwards follow up with you on this because it is a huge opportunity that you have now, and we would like to take advantage of it.

Dr. Swedo: And the second issue is the

question of intramural research. Here, again, we are progressing a bit more slowly than some people might like, but in evaluation of the field I think it is absolutely essential. We need to use the IRP in a way that is best intended, and that is for studies that can't be done better in the field, particularly with the difficulty of recruiting patients to the clinical center.

And my own lab is now actually working with the National Institute of Allergy and Infectious Disease, the immunologists there, to begin to examine the question of regressive autism and whether there's an immunologic role there.

So I think those kinds of projects where we need specialized expertise might better happen in the IRP than in the extramural community. Other ones I think are probably better done through STAART and CPEA.

Mr. Shestack: Is there any way to let us know, basically put a dollar-and-cents number on what kind of intramural research areas in autism?

Dr. Swedo: We could get that information for you soon.

Mr. Shestack: I mean it would be a useful benchmark to have.

Dr. Swedo: And we'll get it done for you, current as well as projected.

Dr. Insel: Andy?

Dr. Shih: There is just one thing I would like to add to my comments. One is that I think that the other major issue I think that's probably true for all the voluntary sector is that, obviously, I think we are anxious to have solutions that are derived from the lessons learned from biomedical research to be made available to the community. Certainly, I think translational research is very important.

NAAR is, obviously, working with the federal government and other voluntary organizations to help implement this public/private partnership vision. Certainly, we are investing in several key areas in autism research that we strongly believe in, such as early diagnosis genetics and, along with NIDCD, language communication issues and development of evidence-based intervention and treatment strategies.

But we see a great need to perhaps receive guidance and help, maybe even from this Committee, to help compile the information and lessons learned from these efforts, and part of this certainly could be data management. But in terms of extracting lessons learned from this, that could help us speed solutions in the community and to further support translational research. So that from the bench to the bedside there could be as smooth a continuum as possible. Ultimately, I think that is what all this effort is going toward and I think the role the NIH and IACC could be to help us facilitate this kind of translational work.

Dr. Insel: So just to respond to that, I think it is a very important point and it may be going forward to a place where this partnership could play out to maximum benefit. Because what we have seen in cystic fibrosis and juvenile diabetes and in other areas of rapid research is that it is often the voluntaries, it's the advocacy groups that do really help in a very vital way for that translation to take place. They're the ones that

can actually bring the families, do the information dissemination, and sometimes change practice just through education.

So I'm not sure right now we actually have something we need to disseminate, but going forward I think the next stage of this kind of public/private partnership could play out just the way it has in other disease areas.

Unless there are other comments, I think we had better move on with a close eye to the clock, but this has been a very interesting discussion and it is a chance to really, I think, use as a benchmark that we have made significant progress, at least in terms of collaboration, and the next question will be what this delivers. We will be looking at this over the next couple of years.

Let's move on before the break to -- although, Jose, it's up to you, if you want to take a break now and do it afterwards?

Dr. Cordero: Why don't we take a break now?

Dr. Insel: Okay, let's take the break. Let's make it brief. We will reconvene at 10:30 and go on from there.

[Whereupon, the foregoing matter went off the record at 10:21 a.m. and went back on the record at 10:31 a.m.]

Dr. Insel: If I can have you take your seats, please? Okay, getting started here, Dr. Jose Cordero is going to introduce the CDC Listening Sessions and Autism Awareness Campaign. Welcome, Jose.

Dr. Cordero: Right. Thank you, Tom. Good morning, everyone. We are going to be talking about two activities that CDC has been involved. The first one is actually the Listening Sessions.

Just as background, Dr. Julie Gerberding is quite engaged on the issues of autism and has asked the CDC staff to have a series of sessions with parents and the autism community to learn what is it that CDC, what else can the CDC be doing to move forward the issues of autism. We have held several, and you're going to hear about them, but what I will do is just simply introduce Dr. Coleen Boyle, who will be describing the Listening Sessions.

I'm just going to take this opportunity also

to introduce her in her new position as Director of the Division of Birth Defects and Developmental Disabilities. She has been with us from the beginning of the Center, first as Associate Director for Science, and she has taken this new task. It also means that she and her Division is where all the activities related to autism are located.

So we are very, very pleased to have Coleen Boyle as Director of the Division of Birth Defects and Developmental Disabilities. Coleen?

Dr. Boyle: Well, good morning, everybody, and I am delighted to be here and also to be able to present to you about the CDC Listening Sessions.

As Dr. Cordero mentioned, Julie Gerberding, our Director, really tasked us with gathering information from the public, from advocacy groups, from researchers and others, to get really wide input into the CDC's research agenda for autism. This is really part of a larger effort that Dr. Gerberding is heading many of you may be familiar with.

We are sort of reinventing ourselves both

functionally and organizationally through a process called the Futures Initiative. Key to that process is really this idea of getting outside input into research that CDC is conducting.

We actually in this process -- actually, this wasn't even planned the last time we met, the IACC met back in May. So this is really all new, a new activity and a new initiative that I'm reporting.

But in going around and doing these Listening Sessions, CDC really used the auspices of the IACC and the IACC research agenda as a basis for public comment. Although we did point out to the audiences as we went around that we were really just seeking input for CDC's portion of that research agenda, but, obviously, we gathered a lot more information beyond just what falls under CDC's agenda.

So just to give you a little background, we conducted four meetings throughout the country, one at the University of Miami in Florida, one in conjunction with the MIND Institute in Sacramento, California, one that was associated with the Autism Society of America Regional Meeting in

Indianapolis, Indiana, and then the last one was actually most recently in New York Sunday in conjunction with an autism meeting at Mt. Sinai.

I actually participated in two of these, the one in Florida and the one in Indianapolis, and there are several others of us, Jose, Marshalyn, Cathy Rice, who are in the audience, who were at the California and the New York meetings. I have to say, too, that Audrey Thurm I believe also attended the one in New York on Sunday.

Just quickly the process: This was really a listening session. What we had was a very brief presentation on CDC's component of the IACC research agenda. So this included presentations by folks in my Division, the Division of Birth Defects and Developmental Disabilities, on the CADDRE-related activities I think you all heard about, as well as presentations by our National Immunization Program that were vaccine-related research.

Then this was followed by a fairly long process where we allowed the audience, under a facilitator, to provide input to that. I think

many people were a little surprised by the format, but the facilitator actually was very good in terms of keeping the process moving and also explaining what the agenda was.

Then this was followed up by a wrap-up by Dr. Dixie Snider. I should mention that Dr. Snider, who is the Chief of the Office of Science for CDC, actually went to all four of the Autism Listening Sessions. So this really is on our Director, Dr. Gerberding's plate in terms of importance.

We also had a process which is continuing for additional input. This included comment cards that were made available for people who might not feel comfortable sharing their comments in public as well as a website where they could actually provide information.

So I'm just going to highlight for you some of the major themes. This is by no means conclusive. We are in the process of developing a more formal report from this, and we, obviously, just conducted the last one on Sunday.

But the suggestions really fell into five broad areas, those being research, and this is

research around etiology, surveillance, and treatment. There were vaccine-related concerns, issues related to public awareness and education; those related to early detection, diagnosis, and intervention, and then the fifth one was suggestions/questions around the issues of insurance and service provision.

So I'm going to highlight some of what we consider right now the key issues around each of these theme areas, but, again, don't take this as final, but I did want to kind of highlight some of these for you to give you a flavor of them.

Around the area of causes and etiology, there was a clear recognition by parents, providers, advocates of the strong genetic linkage for autism and a call for continued research in that area, but also the acknowledgment that they felt there were other factors impacting the increased genetic risk, and that we should not just concentrate on that, but we should concentrate on sort of the gene environment aspects.

Related to that was sort of gender-related issues, you know, the acknowledgment by families

there that there was a preponderance of males affected with autism and, again, the suggestions from that of, you know, take that as a key finding and concentrate studies and efforts in trying to address those.

Issues of comorbidity, trying to understand what the comorbidity issues are around autism, as well as taking those ideas and perhaps looking for common underlying mechanisms there; and, also, an etiology, we heard sort of this urging to look beyond just vaccines, although clearly there was a strong voice as well for vaccine-related research.

On surveillance or tracking or monitoring the prevalence, one of the issues that came up at least at the two sessions I was in was the issue of the difficulty of understanding the prevalence of autism and the need to do community-based sampling to determine what that prevalence is, as well as, since we had two locations where we had many Latino families, the question of whether or not the prevalence of autism really varied by ethnic minority groups.

Treatment was a really big issue. There was an

urging that we develop best practices that are communicated very effectively. Then there was also an urging for us to take seriously the suggestions by parents in terms of alternative therapies, whether these be nutritional interventions, different diets, megavitamins, whatever those theories, whatever those prevailing theories are or therapies are, that we look at what could potentially be the best and brightest and test those out on an evidence-based level.

Vaccine-related issues, there were a number of these. One of them was -- and, again, some of these are not research-related issues, but there was a call to make sure that we have mercury-free vaccine. This really revolved around the fact that this year the flu vaccine continues, some flu vaccine continues to include Thimerasol.

There was an issue related to sort of a perceived conflict of interest at CDC between promoting vaccine and then studying its safety, and that there is a need to take a look, serious look, at whether or not we need to separate those two activities in some way.

The two sessions I was in, and I know the others because I read the notes at least from the California one, there was a clear suggestion that we need to work on repairing the distrust between some parents and CDC around the issue of vaccine. Then also the need to operate transparently; that is, making CDC's data available in a timely way to outside researchers.

Finally, the issue of reevaluating the safety of the current immunization schedule for children.

Around the theme of public awareness and education, clearly, the need, there was a suggestion that there was a strong need for increased public awareness for autism, and, hopefully, you will hear more about that from Kate in a few minutes; the need to educate teachers both in terms of understanding autism signs and symptoms as well as to educate teachers on what is the most appropriate way to educate children with autism.

Social skills, training as part of school curriculum was suggested not just for children with autism, but also for children in regular

education who had paralleled the children in mainstream in terms of trying to understand the differences between children.

And then this was another one that continued to come up, and that is for CDC and others to recognize and treat autism as an epidemic or as clearly a very urgent health problem.

In terms of early detection, diagnosis, and intervention, again, the need both for increased awareness and to educate health care providers and parents about early diagnosis, referral, and effective treatments; just really trying to get that information that is available out there in a consistent way.

This one was a big one, the next one listed. That is the use of a clear and consistent definition and diagnostic code for all agencies, you know, between social services, education, and health. We need to have uniform definitions that a child can't be just eligible for services up to the age three and no longer be eligible for those services. So that message was really heard loud and clearly.

Another one is that parents felt that we needed to listen to them, and "we" meaning sort of the "collective we" here, both practitioners, scientists, others, that they know their children and they don't want to be patronized.

And, finally, it was suggested that we use the experience of children who have recovered to potentially suggest promising interventions or treatments that can help guide us in some of the work that we do.

Finally, around the issue of insurance and service provision, there's a lot of issues around this one. Clearly, families only qualify for service or for some services if they're low income.

There was the issue of limited coverage and availability of services, particularly specific types of services were mentioned such as speech and occupational therapies; variability in terms of the availability of services, and in rural areas services being less available and having longer waits, and then the fact that alternative services are not covered by insurance and that

leaves many families paying out of pocket for these services.

So that just kind of gives you a flavor for the kinds of issues that we heard. Clearly, a lot of them, since this was really the objective here to get feedback on our research agenda and many of these fall outside of the realm of research; this is really what we thought of as our next steps. Those comments that fall within the CDC's purview, we will consider in developing our research priorities.

There were many suggestions that were mentioned that really are not within our purview, are still research that we would like to provide back to the IACC in a more formalized way in the future, as well as to other relevant agencies that might not be represented around this table.

As a first step, Dr. Gerberding has a sent a heads-up letter to many of you and many of your agency heads about the need to work together in addressing these concerns.

We are in the process of taking a better look at this information and trying to come up with a

summary report that we are going to give to her in mid-December. Then we're also sort of strategizing amongst ourselves in terms of really what the next steps are for continued public engagement around these issues.

We all felt this was a very, very valuable process and that we hoped that we can continue to set up a mechanism by which, as several of the earlier speakers talked about, that we can have a really valuable interchange between public and private partnerships here.

So thank you.

[Applause]

Dr. Insel: Thank you.

Do we have questions?

Dr. Boyle: I would be happy to handle questions.

Dr. Insel: Lee?

Mr. Grossman: I just have some comments because I want to congratulate the CDC for their excellent work. The facilitator that they had was superb.

This is the third type of town meeting

listening session that I have personally been involved in over the last couple of years. I did two with NIEHS in the last couple of years.

The impact on the people that are there is quite overwhelming, particularly the parents, to have these government officials come and listen and engage with them. The comments particularly that we got from our Biomedical Conference in Indianapolis, that was kind of what really set this conference above and apart from any other biomedical conference, was the fact that the federal government, the agencies were there to participate, to listen, and to interact with the parents and with the other professionals that are there.

The response from those participants was overwhelmingly positive. I would encourage the CDC to continue this type of outreach as well as all the other agencies that are sitting around this table. I think it is vital to continue this type of dialog, listen to what is being said in the public realm, and then, as the CDC has presented with their next steps, I think those are very

positive steps to move us collectively as a community forward.

Dr. Houle: I just have a very brief comment. I have a brief comment about the unfortunate association of the words "autism" and "vaccines" because I think that has led to a lot of public hysteria over the safety of childhood vaccines. I think that is really not where we want to go.

Even in your slide you talk about autism; you relate the two. I think it's more correct to talk about some of the components in vaccines. It may not just be Thimerasol. It might be one of them. But rather than to say "vaccines in general," you know, because really you have to think in terms of how the layperson is going to look at this. If they see "vaccines" and "autism" in the same sentence, I think that that is really detrimental.

Dr. Boyle: I appreciate that comment. Actually, I did some editing of this on the plane up this morning and actually had some word-specific like Thimerasol and MMR, so specific aspects of vaccines.

I guess in my feeling of listening to parents,

you know, those are subtleties, and I agree that we need to help parents and others understand that we are looking at components of that and that we don't want to classify all vaccines together.

But it's clearly, in hearing from parents, it's clearly a very important issue to them. So I think they were grasping to try to gain our trust, and likewise, to work together on this issue. So, for me, that was the key issue here.

Dr. Insel: Jose? Yes?

Dr. Cordero: Actually, let me introduce Kate Galatas from here. The next session is going to be on the Awareness Campaign, and we have been updating IACC on the progress of the Autism Awareness Campaign from sort of the planning, and now this would be more, it's going to be sort of the rollout that we are expecting to have in February.

Sort of as an introduction, I would like to point out that the Awareness Campaign is one component of what is really an autism program that is really trying to change the way we see the issue of autism, from the point of view that we

are really trying to get at, that health care providers and other providers recognize the early signs of autism and that children with autism actually get an early diagnosis and early interventions, so actually they could do it as best as possible.

I think that is also going to give us an opportunity of having a large cohort, as this program becomes effective, in ensuring that we have a large cohort of children diagnosed very early for a number of other important follow-up studies and answer questions of treatment.

But you are going to be hearing about it, that front-end aspect of how are we going about trying to increase awareness about autism both in the general public and providers.

Kate Galatas will be presenting the Awareness Campaign. Kate has been working with us for a number of years as Deputy Associate Director for Communications in our Center, and she just moved to Louisiana. But I'm so glad that she stayed on and is working with us and the Campaign.

Dr. Galatas: Thank you, Jose. I appreciate it.

I also appreciate the important context Jose gave to where this campaign fits in with the overall programmatic elements at CDC and our Center is doing around autism, because, you know, by the nature of the beast, the communications campaign is the high-visibility piece but it really is only one of many important pieces. So I appreciate the context.

I also want to say that I'm really honored to be here with you all today. This is the first time I've been to an IACC meeting. I was very impressed and touched by the former presentations, including the video from Lonnie and his consortium, that really brings it home to me, having worked for a year and a half or so on this campaign, the importance of what we're doing in trying to help parents and providers and others identify early signs of developmental delay and educating parents about developmental disabilities. But it also drove home the complexity of doing that. So it is very challenging work that we're all doing.

I have heard that this group has gotten some updates on the campaign before, so I'm going to

kind of whiz through a lot of this to get to where we are now. Some of the background, of course, is always important, the objectives of the campaign.

Here I'll really say that we're focused on educating parents on key developmental milestones, what to be watching for in terms of their child's overall healthy development. We want to increase awareness among health care providers and child care providers about the importance of early intervention and identification and diagnosis around treating developmental disorders.

We want to really stimulate parent/provider dialog that moves us past what we have heard the parents and providers are somewhat entrenched in, and that is, as you all well know, the conversation of, "Let's wait and see," "Boys develop more slowly," this kind of dialog, and kind of spur that dialog to another level; and then also increase early action. I mean, the bottom line is we need things to be happening, behaviors to change, and education levels to change related to all of these issues.

Primary audiences: parents of young children

four and younger and health care professionals, child health care professionals; obviously, pediatricians, but also beyond that.

I mentioned child care providers earlier, and they're really a secondary audience. All that means, for the purposes of the campaign right now, is that we don't have at CDC as clear of an infrastructure to work with this community at a national level as we do with, say, pediatricians because we can work through AAP and AAFP and other groups. So there isn't as clear-cut of an infrastructure for how we communicate and what their needs are. So we need to spend a little bit more time, which we have been doing, exploring how to meet the needs of this audience and maximize their utilization and their resources in terms of seeing children in a whole different context than any of the other audiences really do. So we're working on that as well.

The vision and the call to action: The vision is really that: it's time to change how we view a child's growth, again, getting back to the idea that parents/providers need to be aware of

developmental milestones and overall healthy development, not just focused on the interaction around the physical development. The call to action is learn the signs, meaning learn the signs, the developmental milestones, and when you see delays, act early.

The component of our campaign that has been launched already is the outreach we're doing with the health care professional community. We started back in the early parts of the summer with this actually is an e-card that has gone out to now over 2 million health care professionals, again, kind of giving them the part of the message that we want to convey, but also letting them know that more information will be coming their way.

We moved from that in the early summer to -- oh, let me tell you, we moved from that e-card and that awareness-building that something was coming to the development of resource kits. We are working now to get those resource kits in the hands of pediatricians. Inside the resource kit they find a variety of materials: posters for their examine rooms; posters for their waiting

rooms; fact sheets on milestones at certain ages, months, all the way up to five years; fact sheets on developmental disorders, things like, of course, autism but also cerebral palsy and we have a number of other ones; information on resources national and otherwise, resources where they can go for more information and connections, even trying to help them find connections, for example, referrals, how they can do referrals locally.

And then informational cards, and these cards are meant -- this is actually a picture of the little cardholder that is supposed to be placed in a waiting room and on the side where you see this blank spot is an informational card that the parent can take out. The informational card is really a way to kind of give parents who are right there in the mix, they're going to bring their child to see their doctor, give them some level of information to start the dialog.

Again, it talks about things like, by the end of six months, my child should be able to do some of these things: turn head when name is called; respond to sound with sounds; enjoy social play

such as peek-a-boo. This is really meant, all of the materials, I want to say, are really meant to spur the conversation. They're not meant at all to be materials to be used in screening and they're not positioned that way; information to spur a conversation.

The other thing about the informational card is at the bottom we put information, "questions to ask your doctor," and things like, "What can I do to keep track of my child's development," "What should I do if I'm worried about my child's progress?"

One of the things that we found out in our research with parents around this campaign was that they felt like they had gut intuitions that maybe, if something isn't right, how am I supposed to talk to my doctor about this, because they were afraid they would be seen as paranoid or just overly concerned parents and that type of thing. So we took that and we said, okay, we can provide them with some level of information to start that conversation by prompting some questions.

We have about 3,000 of these kits out on the

street that we've distributed via at this point mainly conferences, professional conferences. We were at AAP, AAFP, American College of Nurse Practitioners, and a few other conferences as well. We are going to the Zero to Three Conference in December, and we are also going to be reprinting, obviously, these kits in a larger number as soon as we get clearance. At that point we will do a dissemination plan that clearly is not just go to conferences and hand them out, but much more targeted at and work with our partners like AAP and others to get these into the hands of providers in a way that they will be inclined to look at it and, more than that, use it.

Just so that you know, all the materials that we have are all also available in Spanish. That is a recent development. We had some original materials included in the 3,000 packets that we have out now that only had a few pieces that were in Spanish because we did not have clearance for all the translations, but now we do. So on the website, as well as in the future copies; everything is printed one side English, the other

side Spanish.

Where we're going now: I've told you a little bit about the component that is launched already and that we are actively working on where we are going. Our Direct-to-Consumer Campaign, meaning our first attempts to really reach out to parents of children four and younger, will begin, as Jose mentioned, in the early part of 2005. We are going to do a very staged launch of this component, so that we will see levels of activity and media exposure over time. So between February and May, we hope you will see a whole lot about this.

We are in development of television PSAs, radio, and print. Again, the idea here is to juxtapose something familiar, something they would normally be looking at as a milestone, like when their child might get their first tooth, and combine that with another milestone that maybe they aren't aware that they should be looking out for; again, back to some of what Lonnie was saying earlier, that social babbling.

I should say we are going to try to do some paid placement, but that will be very select,

given the budget that we have and the expense of actually doing paid placement in a national campaign. But we also have a very aggressive kind of earned media approach, so we will be working with partners both in the autism community as well as partners in the private sector to really kind of get more stretch on this campaign in the placement that we get.

I already said all of this. On the child care provider end, I mentioned that we are not in the stage with this where we are in materials development, for example, but what we are really looking at are, who are the national-level partners that we should be reaching out to, including in this? We are starting to learn who some of those folks are.

For those of you in this room who may know who some of those are, I would love to hear from you. This is actually one of the components that I've actively researching right now.

So we're pursuing those national-level partners. We intend to do some targeted outreach to trade publications that this audience would

obviously look to as a source for information. Of course, in addition to national-level partners, we're also looking at federal agencies that are also, of course, national level as well, but more on the home front of federal agencies like ourselves who would be working with this community.

As you can imagine and alluded to earlier, it is very hard to get your head around how to communicate with an audience that doesn't have as many national - level professional associations kind of unified. So it gets to kind of a state-by-state level of how things are done. So it gets a little bit more complicated, and we are going to be pursuing this because we believe, both from the research that we've conducted but also just from your own kind of common sense, you realize that child care providers see children in a social context that we don't get to see.

I talked to Lonnie in the break, and I said, "You know, it was so interesting to watch that video," because to a parent who doesn't ever get to see the comparative view, I mean I have a two-

year-old son and I could have easily fallen into the group of parents who wouldn't have noticed that younger child, that second child, was developmental delayed. I mean, it's just very complex what we're talking about.

Dr. Insel: Kate, we're going to need to move on because we're about 40 minutes running late. Sorry.

Dr. Galatas: Oh, only 40? We're going to continue to engage our partners, and many of those partners are at this table. I haven't had a chance to meet all of them, so I'm happy to be here and be able to do that. We will be doing evaluation of our campaign, so process measures and outcome measures, and this is a very complex component, as you all can appreciate.

Here are our partners, and I'll leave with that slide and say that it has been a real pleasure of mine to work, and to continue to work, with these partners and others as we move forward on this important work. Thank you.

[Applause]

Dr. Insel: Thank you.

Dr. Landis: One thing that occurs to me is that there are a number of relatively large health care/health maintenance organizations like Kaiser Permanente which could serve also as another source for dissemination to reach a large number of pediatricians and big practices.

Dr. Insel: Very good. Well, it's a lot of progress, a lot of excitement. This is really a good update from what we heard at the last meeting. We need to move on to try to capture a little bit of the time we have lost. I want to ask Alice Kau to kick off the introductions for the updates on Centers' activities.

Dr. Kau: All right. I will give you quick two updates on CPEA's activities before I introduce Dr. Volkmar for his exciting presentation.

The CPEA network continues to work very hard on individual site projects at each Center and also to conduct network projects. The newest network project that is being planned for is going to focus on gender differences in autism. This is another good example of how a network like CPEA can conduct research that might be difficult to do

or impossible to do at each individual site.

The newest Committee that was established within CPEA is the Research Dissemination/Public Relationship Committees, and the goal of the Committee is, obviously, to disseminate CPEA science. There is a tremendous amount of science accumulated in the seven years of CPEA's history, and we want the public to know more about it.

Today we are very excited to have Dr. Fred Volkmar to come to give us a science update on the first five years of CPEA. Dr. Volkmar is a child psychiatrist and the Director of a CPEA Center at Yale University. He is very instrumental in setting the best practice in autism work for child psychiatry.

I really appreciate him coming here, and the slides that he is going to show you are just the tip of the iceberg of the science that is being produced by the CPEA network.

Dr. Volkmar: Thank you very much. Let's see if we can get our thing up and running.

Dr. Insel: Fred, we're going to have to add you to this Committee. You're almost at every one

of these meetings presenting.

Dr. Volkmar: I'm going to be very fast because I know what it is like to run behind. Let me just say it is a pleasure to be here again. In fact, I'm "Sally Rogers." Sally was supposed to be here. So I'm covering for Sally. So think of me as about a foot and a half shorter with a pageboy haircut, a laid back Californian as opposed to uptight Connecticut-type person.

[Laughter]

I'm delighted to be here. I was actually giving a talk yesterday to 200 pediatricians in Albany, New York. I'm reminded I'm actually not on my computer, which is good, because in the middle of my presentation up popped a heated IM exchange between my daughter who is "pink333" and "vanillabean456" about some hot kid in the Latin class. So I'm glad I don't have to deal with that.

[Laughter]

Lastly, let me mention, as we get started, Lonnie mentioned earlier the lead article this month in The American Journal of Psychiatry is in article on autism in a 15-month-old child. In

fact, this is a child we followed from two weeks of age. If anyone is interested, I'll leave some copies out there, but, indeed, it speaks to the whole issue of the tremendously increasing interest in autism in very young children.

I want to very quickly go through some of the highlights of the first five years of the CPEA program. CPEA is based at a number of sites around the country. This shows the main sites. In fact, if we were coloring in additional states that are additional ancillary sites, we would have, I think, five or six additional colors there. It's not just red and blue, which is important to realize, but that, in fact, we're spread over the entire country; that over these years we've, in fact, evaluated over 4,000 children, including over 2,000 children with autism spectrum disorder.

One area of work has been very much focused on diagnosis and early detection. You've already heard a little bit about this in terms of our work on methods for toddlers and young children, but also a growing body of work in identifying symptoms of autism in children under a year, and

issues of differential diagnosis which are very important, as you heard in the last talk, in terms of intervention. And, finally, longitudinal stability issues, having identified children very early and identified children through screening, the important thing is to be able to say how much this persists or not over time.

A whole series of studies have been focused on characterizing the phenotype and course in autism, looking at specific aspects of the core social deficit. The last time I was here I talked about face processing. There has been a collaborative project on regression in autism and its relation to outcome; studies on abnormal movements, for example, in the face, and subtypes of language difficulties.

Studies of the broader phenotype are an important emerging area in terms of genetic research. Paradoxically somewhat, as we've realized we can now define the core autism in a very serious and rigorous way, we have now gotten interested in the broader phenotype of autism. Our group in the CPEA has worked on developing

measures for defining the broader phenotype in parents and sibs, looking also at younger sibs, as you have heard about, and also looking at parents to discover the potential phenotypes: face processing, ERP measures, other kinds of measures and, finally, also looking at particular brain structures in parents.

Speaking of brain structures, people have been looking at specific abnormalities in several areas, the enlarged cerebral volume, which we've talked about; abnormalities in CSF white and gray matter; abnormalities in the white matter of the corpus callosum, and other abnormalities, including the amygdala.

Neuropsychological deficits have been identified, including prefrontal impairments in terms of working memory, attention shifting and response, in addition; medial temporal lobe impairments, for example, tasks which happen in the mentala and hippocampal function, and face processing impairments. This has been a very active area of work in the network.

The nature of face processing deficits has

been very extensive study. In fact, here is one of my colleagues, Bob Schultz, MRIs. FMRI studies have looked at prefrontal cortical and singular abnormality d**u**ring working memory tasks. The fusiform face area in particular has been the object of great investigation, and atypical activity in brain regions related to word processing, and decreased activity in regions related to prosodic cues and facial emotions.

This is a very interesting and emerging area, one of the things that's been identified in autism since Lee/O'Connor, the characteristic deficits among people with autism who do talk and their prosody of the musical aspect of speech, that tendency to talk like a robot that often is very stigmatizing for people with autism. In fact, there are studies now at several different levels for both younger and older and higher-functioning individuals trying to understand more about the nature of this problem, and also studies looking at synchronization in terms of functional under-connectivity, which we heard about earlier. And new software analysis methods have been developed

for the FMRI studies.

Studies in ERP and MEG, eye-tracking studies, have looked at very young children to look at abnormal ERP responses to face, emotion, and speech, adults with autism versus those with Fragile X, the initial different patterns in the ERP responses to auditory stimuli.

And, finally, individuals with autism using different patterns of gaze in social situations; this is some of the eye-tracking work that we at our Center, but also Jerry Doss at the University of Washington, have been doing.

Finally, some studies on auditory processing have also been undertaken using MEG.

Animal models work has gone on using lesion studies to clarify the role of early lesions in the amygdala and orbital frontal cortex in the development of autistic-like symptoms, and parallel deficits in eye blink conditioning in autism spectrum disorders, animals with prenatal valve port exposure which affects the expression of the Hoxa gene. This is Patty Rodais' work.

Etiology, people have been looking at the

phenotypic consequences of chromosome 15 through duplications and their variability, a number of other brain regions as well including tryptophan hydroxylase. The lesions in chromosomes have been discovered in autism multiplex families, and a candidate gene list for autism spectrum disorders has been developed from studies of chromosome rearrangements.

Over 250 multiplex families have now been assembled for linkage analysis. The Hoxa gene allele was discovered as a marker for autism spectrum disorder and associated with macrocephaly by Patty Rodais and her group. Another gene has been associated which is potentially a target for that Hoxa1 allele.

A second drug, mosoprostil -- right? -- has been identified which identifies a risk factor for exposure for media syndrome which Patty has worked on.

Intervention studies, we have been concerned with factors related to longitudinal outcome, and doing clinical trials, randomized clinical trials, controlled trials, that demonstrate large effects

on joint attention and symbolic play from short-term intervention. This is work at UCLA by Marian Sigman, Connie Kasari, and colleagues.

And, finally, studies looking at the importance of parent behavior in promoting and consolidating child language disorders and, lastly, I should mention two studies have shown that secretin was not, in fact, effective for reducing symptoms in autism.

Finally, this shows some of the network projects when we were originally funded. We were funded as individual sites. In fact, one of the nice, exciting developments over the first five years, which is now continued with the change in our mechanism, is that a number of collaborative projects have been undertaken, and this is a partial list. As you heard from Alice, there are actually several new ones joining this list right now.

And thank you very much.

[Applause]

Dr. Insel: Thank you, Fred. Unless there are comments or questions, let's go ahead and hear

about the progress in the STAART Centers, and Deborah Hirtz will take us through that.

Dr. Hirtz: Sorry. I don't want to waste time trying to get hooked up here. I know we're a bit behind schedule, and I will try to be pretty fast.

So I'm just going to run through the first few slides and try to spend a few minutes explaining some of the different intervention trials particularly that are going on in the STAART Centers. So these are the participating Institutes and Centers, which you've all seen before. So I'll go through them quickly.

We have eight Centers, two of which have been funded for over two years and six of which have been funded for over a year. Our Data Coordinating Center is DM-STAT in Boston.

When we met the last time, we were just before the Joint CPEA and STAART meeting, which was held here in Bethesda. These were the different symposia that took place at that meeting. In addition, there were a number of different working groups that got together and discussed areas of mutual interest and possible collaboration, as

well as scientific meetings for both the STAART and the CPEA networks, scientific advisors' meetings.

In addition, we have had and are planning a number of other meetings which have been, I think, very important and vital to the function of the STAART network. There was a very useful meeting just this month in Boston.

What was discussed was really what it means to be a network and how to implement some of the recommendations that the scientific advisors had given following the last meeting. Those recommendations at least centered around items such as increased communication and visibility of what the network was doing both to the public and to other investigators outside the network, increased ability to share data not only within the network, but in general.

Other areas included more focus on the phenotypic characterization of subgroups in autism. Can we learn more about girls, about minorities, from having such a large dataset available? Other things included just generally

things that were related to increased collaboration and increased discussion of the big picture and where things were going.

Part of this discussion led to a meeting which will take place Monday for all of those in the network who are interested in talking about and planning new intervention studies as well as another meeting in the spring for anyone involved in any aspect of the networks -- it doesn't have to be intervention studies -- to get together and exchange scientific ideas and plans to plan future studies.

So these are the DM-STAT activities. I've been working very hard on getting the core measures up and running, so that all the sites can put their data into that format. They're maintaining a STAART/CPEA website, individual network websites as well as developing a public website. They are doing the support for the clinical trial, that is, randomized clinical trial, of citalopram that's been ongoing and successfully recruiting, and various other functions.

So what follows is a listing of the STAART

projects. Again, because of time, I want to focus primarily on the intervention ones, but there are four genetics projects which are not intervention projects related to repetitive behaviors gene finding, speech and language and facial expression. There are mouse model projects. There are six different imaging projects, and there are, again, plans for discussion and collaboration and thinking and brainstorming about ways to pool some of that data.

There's neuropathology. There are four projects on early development, three on early detection, and one project characterizing the broader autism phenotype. Now for the intervention projects, there are two that focus on early intervention and behavioral/dietary and pharmacologic. So the early intervention projects, the first one is at Kennedy-Krieger that is looking at, I believe, four groups of children. One is the sibs of children with autism, and these children are around two years old. They're being observed in the classroom. So there are siblings. There are children who have been diagnosed with

autism at a very early age. The third group is children who have been diagnosed with a language or speech impairment, and the fourth is a group of normal controls.

The trial, the study that is taking place at University of Washington regarding early intervention is a randomized control trial looking at children who receive early intensive behavioral intervention and those who receive standard community therapy. One of the measurements, outcome measurements, in that trial includes measurements of brain action, of brain action potentials and brain electrical activity.

So in UCLA there are, in addition -- well, I think actually, as Fred mentioned, as part of the CPEA networks but also as part of the STAART network, a project on peer-mediated interventions for improving social skills in children with autism.

The other project that is listed here is not actually an intervention project, but what it is is it's observational, but looking at the factors which seem to predict success in response to

treatment. So that is also information that is very important to get in order to make some advances on how to best administer treatment.

Another trial at UCLA is a parent-assisted behavioral training program. This teaches social skills to high-functioning children with autistic spectrum disorders. The outcome measures on this trial include how the parents observe the children, how the teachers observe them, and also how the children feel about themselves and their self-esteem.

The intervention trial at Yale, again, I think Fred also touched on, but a very important one as part of the STAART Centers is the "let's face it as a game" to teach children more about how to pay attention and how to observe faces and focus on faces. One of the interesting things in that trial is measurements not only of the eye tracking to see if they're doing it better, but also looking at functional magnetic resonance imaging with brain oxygen levels, the bold scans, and seeing if certain areas of the brain that should be activated with face recognition, mainly the

fusiform gyrus are activated after this gaming therapy.

We do have one diet trial that is very important. These children are given a gluten-free, casein-free diet. This is at Rochester. They are given blinded snacks, cookies or something like that, that may have nothing in them or may actually have a challenge with the gluten or the casein, and then they are observed by a blinded observer to see if it makes any difference in their behavior. That is recruiting now as well.

In progress there is one large multi-site trial, and that is the citalopram treatment for high levels of repetitive behaviors in children who are between the ages of five and seventeen, and that is a blinded, randomized control trial to look at the benefits of citalopram on global functioning in these at-risk children.

In planning there is a second multi-Center trial which will probably start on a very limited basis to make sure of safety and tolerability to treat young children with fluoxetine for effects on the behavioral domains that are significantly

impacted in children with autism.

So there is, as I say, a meeting just Monday to discuss, again, more collaboration and more multi- site clinical trials. I'll stop there, if you have any questions.

Dr. Insel: Deborah, do you have any numbers in terms of recruitment? How are we doing in terms of milestones and targets for recruitment?

Dr. Hirtz: Most of these trials are not very big, but we are doing fine in recruitment. The citalopram trial at this point has 36, 35 or 36, children enrolled. The startup time is always something that takes longer than expected, but I think as far as enrollment we are doing okay.

Mr. Shestack: There are six imaging studies. Are you working on the same initiative that Susan Swedo talked about in terms of finding some way to combine all that data that's going to be coming in new to the system?

Dr. Hirtz: Well, that is something that people are just beginning to talk about, but they definitely are. One of the first committees that got established was the Neuroimaging Committee and

it's actually not just STAART, but joint CPEA and STAART, and, yes, the investigators are trying to figure out ways that they could combine data as well as collaborate on future studies.

Dr. Insel: I want to emphasize that issue because we've talked about it a couple of times here. It does mean a change of culture, but it is something that we need to really stay on top of, this idea that the ultimate answers may not come from the people who have collected the primary data but from a secondary analysis, and in genetics and epidemiology and now in imaging we want to make sure that, to the extent possible, since taxpayers have paid for all of this data, that the data becomes available in the public domain as quickly as possible, to be used by as many people as can get access to it.

So I think having this for imaging is going to be an important advance. It's something we should build into the plans. Let's go on. Jose, perhaps you could quickly update us on the CADDRE centers.

Dr. Cordero: I'll do a one-minute, actually more like two minutes, so we can catch up some

time. I guess if I would have to summarize where are we with the CADDRE, it sort of reminds me of the college student that sends a little telegram to parents saying, "Everything's great. My number to send money."

[Laughter]

The CADDRE sites, we actually at the last meeting had a detailed presentation on a case control study and all that it is going to cover. It is going to be very comprehensive, a case control study. We are planning to begin it next year, but the scope of the study will depend on the resources available. Right now we are quite short. That's my report.

Mr. Shestack: Dr. Cordero, I have a question. Last time I think you presented the same message, and my understanding was that, when the CADDRE centers were started, each site had individual studies and then some joint studies.

Dr. Cordero: Yes.

Mr. Shestack: But then a lot of these things never got off the ground because of not adequate funding, is that correct?

Dr. Cordero: Well, actually, the CADDRE sites -- I'll sort of summarize -- they were supposed to be working on three things. One is developing surveillance in their area, which is basically essential for being able to identify children in the study. No. 2, it's that they have special projects and then the collective study of the three.

The first two actually have been happening, and especially the special studies. Actually, all three, but the planning of this case control study is something that takes fewer resources now when we realize that we have to do like a lot of assessment to confirm the diagnosis, et cetera. Then we realized that actually the funding that we have overall available is not going to be sufficient to do everything we could and should do.

Mr. Shestack: But what happened with the last four years of funding that had been allocated for that study?

Dr. Cordero: Actually, developing the surveillance --

Mr. Shestack: Yes.

Dr. Cordero: -- planning the case control study, and working on the special projects.

Mr. Shestack: So it was apportioned elsewhere? Yes.

Dr. Cordero: Well, actually, those were the three intended purposes for the study, and all of them go together. Like the work looking at sort of immune issues and gastrointestinal issues in autism has been done out of that. Early identification is out of that. So we have presented how all those studies have been progressing.

Dr. Insel: Okay, we're going to move on to the next part of the agenda, which are some science updates. Up until now, we have been talking a lot about the mechanisms and the opportunities for collaboration and through progress reports but we wanted to dig a little deeper into two areas. The first will be around just building on what Jose has been talking about, one of the CADDRE projects. This will be from Dr. Craig Newschaffer, who's an epidemiologist with the Bloomberg School

of Public Health at Hopkins. He's the PI for one of these five CADDRE Centers.

It's a nice sort of historical trend here because Craig is someone who comes to autism after a career in the epidemiology of cancer. So this is the kind of thing we like to see, is that people who are successful in one field begin to work in this particular area.

Dr. Newschaffer: Thank you. Thanks very much. It's a pleasure to be here to talk on some of the activities that have come out of our CADDRE epidemiology center.

As was just summarized by Jose, the CADDRE sites had a mandate, as was written in the Child Health Act and was propagated in the RFA, to do three activities: the surveillance, plan for and, hopefully, one day execute the case cohort etiologic study, and conduct center-specific studies.

There actually have been a large number of center- specific special studies that have been done across all the centers, including ours. This slide lists all of the activities that we have

been engaged in, some of them in collaboration with other investigators and some of them supported by ancillary funds from other sources, such as NAAR and NIH. But, as you can see, at least in our Center, there has been a large scope of activities that we have been making good progress in the special studies arena.

I was asked to come here today to talk about one of our special studies, which is the IDDES study. The IDDES study was designed -- it's sort of, after hearing the summary of the CPEA, I felt a little awkward because this is sort of a presentation on kind of the inglorious, yet very important, pilot work that needs to be done before you implement a very large case cohort study like we're planning.

The case cohort etiologic study is intended to recruit over 900 children across all sites, 900 children in the autism group, in the control group, and in a third comparison group. So this is going to be a very large effort. At least for our site, there were some nuts-and-bolts activities that we felt we needed to get in place before we

could transition into this very important multi-site activity.

So the IDDES study was done to establish internal collaborations at Hopkins between our group and the School of Public Health and Kennedy-Krieger. Dr. Landre's group is going to be the clinical assessment site for our CADDRE case cohort activities. We wanted to also pilot some of the data collection approaches that we have planned for CADDRE.

Then the next bullet down is one of the questions that was key to us in deciding how we were going to be recruiting for CADDRE is we needed to look at the performance of some screening tools in the somewhat younger age group, three-to-five-year-olds, which is our target for the purposes of our etiologic aims in CADDRE. So we undertook to do this in the IDDES study.

Then we also wanted to collect some preliminary data on a few domains that were of interest to colleagues in our group. What I'm going to talk to you about today mainly is these two bullets, some of these pilot data activities,

nuts-and-bolts activities, and then I'll talk a little bit about what we found when we looked at the performance of the SCQ in this three-to-five-year-old age group of kids.

So recruitment for IDDES paralleled what we anticipated doing for CADDRE in some respects. For CADDRE we wanted to do population-based recruitment. One of the key sources, in addition to the clinical sources -- we will involve clinical sources in our area for CADDRE recruitment, but those relationships are in place and those sites are used to recruiting subjects for research studies.

In order to expand the representativeness of the sample, we also wanted to recruit through school systems. So we focused for IDDES on school-system- based recruitment. So we had the Departments of Education in the two states in our area do mailings on our behalf to three-to-five-year-old students in special-education. These were all special ed. classifications. We did this in one school district in Maryland and one school district in Delaware.

We collected self-report screening data and some of the other items that I mentioned to you. Then we brought in just a small subsample, because this was a pilot activity, of some of the screened positives and negatives into Dr. Landre's clinic to do some of the components of CADDRE data collection together in collaboration between our site at the School of Public Health and Dr. Landre's site at KKI. We did some behavioral assessments, piloted that maternal interview, as I mentioned; did a subset of the biologic sampling activities that we planned for CADDRE; did medical and education records review, and fielded a paternal questionnaire.

So this is sort of a busy slide. I'll call your attention to two numbers. Essentially, a little over a thousand parents of children in special education in this age group were contacted by mail. We did not have the resources at our disposal to run the full gamut of enrollment contact that we planned for CADDRE. For CADDRE we planned to contact by mail, include incentives, do follow-up mailings, and also do follow-up

telephone calling. This was just a one-shot mailing because, again, of the resource constraints.

What you see is, based on this one-shot mailing, we had about 27 percent who returned and completed the screening instruments, which were sort of the first piece of data collection at the top of the funnel for IDDES. So what do we feel about that? I'm basically encouraged because I think that, with this level of response from this broad population without much effort, special effort, geared at increasing enrollment, I think that we have demonstrated that through the school sources we should be able to recruit sufficient numbers to support, again, those ambitious recruitment goals for CADDRE.

Now, again, the maternal interview, which I know you've heard about, the case cohort study last time, it sounds like, the maternal interview for CADDRE is an ambitious interview. It has sections on a number of different potential autism risk factors. We fielded the full maternal interview draft in, again, our subsample of IDDES

study participant.

This was a very valuable activity, and I won't go through all these in detail, but the piloting of an interview instrument is always informative and sometimes in surprising ways, but a number of questions that we had originally stated in the interview. There were clear needs to make some modifications. This IDDES study activity allowed us to make those changes.

So there were some minor changes such as you see here, and then there are some items that we're still deliberating and revising for the interview. Ear infections, definition of chronic and recurrent ear infections was not clear enough, for example, and we're working on revising a whole set of questions based on the IDDES study activity.

The other thing that we looked at is medical records acquisition because, again, CADDRE has a very ambitious medical records collection plan. We want to collect early-life pediatric records on the pro-bands and we also want to collect labor and delivery records and OB/GYN records on the moms.

So we developed a protocol for acquiring these records, and again for the small subsample participating here we did the sort of, again, the inglorious but important work of sort of tracking fees and getting an idea of how long it took to acquire these types of samples, which was important for the whole group in terms of planning the larger activity.

The other thing that we did is we focused a little bit on buccal cell sampling. In CADDRE we plan to collect blood as well as buccal cells. But one of the things that we wanted to do both for CADDRE and just for other research applications -- there's a lot of interest, of course, in buccal cell sampling, because of its less invasive nature. It, as you know, yields less DNA, but there's work going on in terms of whole genome amplification to amplify the DNA from buccal cell yields, and that work is progressing nicely.

One of the things that we did here is we set up a small experiment, because there are some data coming out of NCI which showed that the way you collect the samples has an impact on how effective

the whole genome amplification is. She has recorded that if you collect the swaps and then immediately dip the swaps in cell lysis solution and then store that solution, as opposed to storing the dried swaps, you get not so much better yield in the amount of DNA, but you get a DNA sample that is more amenable to whole genome amplification.

So we wanted to conduct a little experiment to test that. So our buccal cell samples are going to allow us to do that moving forward.

All right, now I want to talk briefly about the work with the SCQ. There has been some past work looking at the SCQ's performance in younger populations. As you know, officially, it's validated for populations age four and above, and there's a standard cut-point with documented sensitivity and specificity, but in the original paper it says, of course, other cutoffs may be preferable for general population samples such as ours, and choice may also vary with the purpose; for example, screening for case detection versus case collection.

Now Hanson, in work that was reported at the IMFAR meeting a few years ago, looked at a modified version of the SCQ in two-to-four-point-five-year-olds, and it was a fairly small study. She found somewhat less satisfactory performance, sensitivity and specificity, particularly the specificity numbers, in this small sample. Nonetheless, her conclusions were optimistic. So we wanted to take a good look at this in our age group.

So the things that we asked essentially were is greater than or equal to 15 going to be the best cut-point for our purposes of ascertaining cases for a population-based epidemiologic study? So we conducted a number of analyses. Essentially, for those 285 screening interviews that we received back, we looked at three different imperfect gold standards. Now, remember, we did not bring all these kids into the clinic for ADIs and ADOSes. So our gold standards are alloyed.

The first is parents' self-report of ASD diagnosis or an autism special education classification documented. Then we looked just at

an autism special education classification documented. Last, we looked at the special education classification documented plus the DD classification. Now realize that we think that this is probably the best gold standard and this is probably the worse, because adding in those younger kids with DD classifications, they're obviously all not going to be true ASD cases.

We looked at the performance of the SCQ in the all-age group and in the younger kids. We looked at ROC curves, assessed the area under the curve, which is a measure of general performance of the screen, and then used two approaches for looking at optimal cut-points: Youden's J, which balances sensitivity and specificity, and then the index of validity, which looks at the maximum correctly classified. Then we estimated sensitivities, specificities, and predictive values at the standard cut-point and at the cut-points that we ascertained from these analyses.

So this is the ROC curves for the all-age group. The overall performance, especially when we look at what we think is our best imperfect gold

standard, is reasonable, almost 90 percent with a not-too- imprecise confidence limit.

Again, as we expected, when we looked at this other gold standard, which we think is the worse because of the incorporation of this DD which we know is not a good proxy for true autism, the performance goes down, which is, again, not surprising.

When we looked at the younger ages, we see ROC curves, area-under-the-curve statistics, again, in sort of a good range, although I will point out that you will notice we have much fewer events in this younger age group of 69 participants.

Then we looked at the sensitivity/specificity and predictive values. Again, this is in the all-age group using our best, yet still imperfect, gold standard. You can see that in this sample the traditional cut-point yields a sensitivity of 51 percent and a specificity of 92 percent. The Youden's J cut-point, which was 11, yields a higher sensitivity and a little bit of a reduction in specificity. The index of validity had low sensitivity and a very high specificity, which is

not surprising because most of the kids in the sample did not have autism. So it's going to favor specificity.

Now when we looked in the younger children, again, because there were few of the younger children and few events, these sensitivity statistics and the predicted value statistics are very imprecise, so I don't put a lot of stock in them. But we were able to estimate with fair precision specificity, and the specificity numbers at all these cut-points is much higher than the work of Hanson. So we were encouraged by this.

So what did we decide for the CADDRE study? Well, we wanted to be inclusive because this is case finding for the purposes of a research study, and one of the design features of the CADDRE case cohort study is there is this third group, this neurologically-impaired group who do not have ASD, but they do have other developmental issues.

So, in other words, if you're brought in for an assessment under the CADDRE protocol, and you're found not to meet autism, but you still have other developmental issues, there's still an

opportunity to participate. So there's less of a cost for bringing these false positives in under the CADDRE protocol.

So we decided that we wanted to adopt a cut-point below 15 and we settled, based on these data and also some other input from other sources, on 13. This is the sensitivity/specificity and positive predictive value at that cut-point in the IDDES study dataset. That's what we were proposing to use in CADDRE.

Again, we're starting to bring in this small subsample of IDDES study participants for clinical assessment, and I have some data on their ADI scores. Again, realize these are small numbers. The top of the Y axis is 4. But you can basically see that by SCQ score, again, low SCQ scores, the three children who had SCQ scores below 12 are all negative and those who had 15 and above are all positive. We did have this one case right at 13, which would have not been considered a screen positive under the standard cut-point, but was, in fact, positive on the ADI. This individual would be captured under the CADDRE cut-point that we

have decided to adopt.

So, again, the predictive ability of the SCQ appears to be fairly good or good enough for our purposes in this population. In younger children we saw better specificity than Hanson, et al., did. The performance appears to be acceptable with the cut- point adjustment for the purposes of case findings in this epidemiologic study.

Again, echoing what was said in the original article putting forth the SCQ, really the cut-point that you choose depends on the purposes at hand.

The next step for IDDES, just winding up, we're going to complete clinical assessments until we have 50 in hand, 25 from the screen positive and 25 from the screen negative. We can look at these data with regard to screener performance. We will look at the maternal interview data in this full sample. We will do that experiment about the two different buccal swap storage techniques.

We've collected toenail samples and there's been some talk of doing some pilot studies on metals in those toenail samples.

I thank the parents who participated in IDDES, the folks at CDC, and my colleagues at our Center. Thanks very much.

[Applause]

Dr. Insel: One of the questions that comes up around this table is the sense that I think all of us have that this is not one disease; it's a complex collection of disorders that we don't really know how to define subtypes of. In fact, it was mentioned earlier today about the importance of looking at comorbidity and whether that would help us to factor out subgroups.

Is the CADDRE going to take that on in any way, I mean beyond just sort of identifying who gets this label?

Dr. Newschaffer: Oh, absolutely, yes.

Dr. Insel: What's the next step to try to break it down to help with individual phenotypes?

Dr. Newschaffer: Well, there is much more extensive behavioral phenotyping done than we did for IDDES under CADDRE. There's also comorbidity assessment in terms of gastrointestinal, sensory, sleep, dysmorphology. So we have extensive

clinical phenotying to go along with the richer set of behavioral phenotyping.

I really think that the strength of CADDRE is the fact that it's going to be the first time where in a large sample we're going to have extensive phenotyping data on a very large population. We're going to have extensive risk factor data obtained from interviews and medical records, and we're also going to have biomarkers collected on this full sample. So I think this will be the first time that we will be bringing these three very critical dimensions together.

Dr. Insel: Jose?

Dr. Cordero: Actually, I think that this project also intersects with the other work being done in the phenome project.

There's one thing that I would like to underscore, which is that this is population-based. So that actually brings a very important dimension in terms of, as we look at sort of the distribution of the different phenotypes, I think that we will have very robust data and also help the prevalence of each of these phenotypes.

Dr. Insel: Jim?

Dr. Hanson: I just wondered, Jose, is there a component of this that addresses some of the LC-type issues, impact on families who receive, for instance, a tentative screening positive result and the impact on those families?

Dr. Newschaffer: Yes, what we did in IDDES, and this is the approach that we plan to use at our site at least with regard to the screening issue is any child who screened positive who did not have an existing autism spectrum disorders diagnosis -- remember, a lot who screen positive already have an autism special ed. classification -- any child who did not, when we contacted them to inform them of the results, it was not a letter saying, "Congratulations." It was a phone call from a clinician in Dr. Landre's shop, and we had a protocol and a phone script on how we were going to approach this with some sensitivity.

Dr. Hanson: I guess the question partly is—what are you going to do with the data? I mean are there identified or identifiable adverse outcomes that would be appropriate to explore?

Dr. Newschaffer: That's an excellent question. We didn't have a plan for that within IDDES. Again, it was a very small sample. But there might be some sort of a post-identification monitoring that we could do as part of the CADDRE protocol which would be important.

Dr. Hanson: Yes. What I'm suggesting is that, as you scale up to this very large study, that will become an increasingly important issue in terms of public perception, and so forth, and might be remarkably different within different ethnic or other social groups.

Dr. Newschaffer: And original groups, I agree.

Dr. Insel: Thank you very much. We're going to move on to the last presentation of the morning, which will be from Dr. Bruce Devlin, who is coming from the University of Pittsburgh. You've heard already quite a bit about genetics this morning, but this will give you a chance to drill down a little bit more on some specific results related to his work as part of the CPEA genetics network.

One correction: This is Bernie Devlin, not Bruce Devlin.

Dr. Devlin: Yes. In fact, Bruce Devlin seems to be an administrator at the University of Pittsburgh and I get his mail all the time -- very interesting.

Dr. Insel: Well, we had invited him, but he couldn't make it.

[Laughter]

Dr. Devlin: Right, right. So I was asked actually, and it's a great honor to be here to review the state of the field of genetics for autism and also to provoke some thought within this particular area. Who knew that Tom Insel would actually have more late-breaking news than I would about the genetics of autism? So maybe my news will be a little bit dated, but I still think that I can be a little provocative. So I can do at least that.

I wanted to start with one of my favorite quotes from Bertrand Russell which I think has a lot of value as we think about the world in general and science in particular. It's a little bit of a provocative quote to begin with.

"The whole problem with the world is that

fools and fanatics are so certain of themselves and wiser people so full of doubts."

Now there is a caveat from Devlin, which is that those in doubt are not necessarily wise, but they could be.

[Laughter]

I want to bring that up — I brought that up because I want to underscore two points about the field of autism genetics. No. 1, actually, how little we can be actually certain of in this particular area. I think it's really important to bear in mind. Yet, how certain I am that we're poised to make great progress in this particular area. Time will tell just how foolish I've been on both points.

All right, so autism, repetitive and stereotypical behaviors, impairment in social interaction, and impairment in communication, we all know about that. What's interesting is that this disorder is so clinically heterogeneous and it displays such a range of spectrum and severity, and we know so little about what's causing this at a genetic level. It's a worrisome thing.

In fact, when you look at family studies, you see a big spectrum of diagnoses. As Dr. Insel was just mentioning, it raises the issue of, is it because we have the same genetic variation that's being perturbed by environment to generate differences in expression or is it because we just lump a bunch of clinically- and etiologically-heterogeneous disorders under the same name because it makes us feel better? It makes us feel that we know more.

That's a big word: in "environment." It was great to hear people talk today about what studies are actually going on in environment. The baby SIDS study is going to be quite important. Some of the other studies, the epidemiological study is going to be quite important. Because really what we know about environment is, in my estimation, dismal.

We know that MZ twins are 9 to 40 percent non-concordant. Many of my colleagues interpret that as meaning that the environment is 9 to 40 percent important in the determination of liability to autism. I would say, well, maybe, but, in fact,

you're totally ignoring development on stability; you're totally ignoring the possibility of gene/environment interaction. Really what that tells us is basically nothing. It doesn't tell us much about the environment. We need to get much more detailed about what's actually going on. We know that some infections can lead to autism-like presentation.

Okay, what, we do know about autism is that it's strongly familial that the recurrence risk is 15- to 30-fold, and many geneticists interpret these data as meaning that there's 70 to 90 percent broad sense heritability for autism. I'll discuss that in just a minute.

We know that males predominant over females in terms of diagnosis of autism, and we know that it's distinctly non-Mendelian, as Steve talked about earlier in the day.

So what geneticists have interpreted about this is that what we have in autism is interacting genetic variants that are determining liability to disease, and that's certainly an explanation.

Where does this broad sense heritability come

from? It comes from the fact that MZ twins are 90 percent concordant; DZ twins roughly 15 percent concordant. Indeed, under an assumed model of the genetic basis of autism in which genes or genetic variation and environment come together in children to determine the liability to autism, that's exactly how you would interpret the data.

But you have to bear in mind that that's your model. Your model is that the genes and the environment in children are coming together to actually determine liability. In fact, what I would say is that it's also compatible with gene by environment interaction with epigenetic models, with mixed genetic and epigenetic models and other models, one of which I'll stress today.

Okay, but let's take on face value the genetic model for just a little bit. Then what it suggests is that interactions between genetic variations in the genome, is terribly important in terms of determining liability to autism. Then those liabilities, when I first got into the field a few years ago, got interested in the genetics of autism, I liked to just ask questions. So I went

to the experts and I said, okay, this suggests that you should have dimensions of liability that we can look at, and if we can look at those, they should be heritable; they should be transmitted between generations.

So are they? Are social deficits transmitted between generations? Are the parents of autistic children, for instance, more likely to show social deficits? The fact of the matter is that the answer was not as pleasing as I would like. They said, "Well, maybe." There is some evidence for that, but it's largely anecdotal.

It's really great to hear that, in fact, some of those holes are being plugged right now with studies that are ongoing, because that's a very big hole in the genetic studies. It would help us a lot to have had those rigorous studies earlier because there are some really squishy things about the genetics of autism that we need to understand. This would be quite helpful, in fact, in terms of what Tom suggested for etiologic heterogeneity.

What we've instead relied on as a workhorse for the genetic studies are what I call multiplex

families. That is, families in which two or more individuals are affected with autism. There are nice studies that I can tell you about, relatively independent studies. All of them have at least an ASP, which is an affected sib pair, with autism. Many of them, some of them have extended pedigrees. So the numbers will pop up again on the next slide.

These are the publications. What's on the very right, on your very right, is the number of signals from these genome scans which provide some evidence that a particular region of the genome displays too much sharing among these affected individuals than you would expect by chance. So that's what we're looking for.

We actually distribute genetic markers across the genome. We scan through the DNA. We're looking for excess sharing among affected individuals within families, more than you would expect by chance.

What do we see from these studies? Well, here are 12 chromosomes, 1 through 13. I've skipped 12. You can see the studies are on the left-hand side,

the centimorgan location on the chromosome in the middle, and then the rough linkage score on the right-hand side.

What you can see, although I've missed one, is that we have some locations of the genome in which more than one study has a substantial linkage finding on those chromosomes, chromosome 2, chromosome 7. There are actually two places on chromosome 7 that light up with two different studies. On chromosome 2, three studies find linkage signals remarkably in similar locations. Missed chromosome 1; I'm sure you all noticed that. Here are the rest of the chromosomes, and chromosome 17 gets hit twice. Chromosome X gets hit twice.

So there are some interesting findings that are out there when we work under this assumed genetic model where vulnerability is coming strictly from the children and from the environmental variation that the children experience.

Let me focus for just a minute on chromosome 17. So bear with me because chromosome 17 was very

exciting at the American Society of Genetics meetings and the reason is pretty simple to understand. Analyses of the AGRE sample, which were follow-up studies of the Youden study that I showed you earlier, suggested that there's sex-differential liability in autism. We know that males predominant over females, and so they had this very interesting approach to dividing the data. That is that they divided the families into families that only had male children affected and families in which there were at least one or more female children who were affected.

What they found was that there was an amplification of linkage on chromosome 17 Q11, in fact, big amplification of the linkage signal on chromosome 17 Q11, in these male-only families. So that's a very interesting finding.

One of the reasons it was interesting and caused some excitement because it sits over top of the serotonin transporter. The serotonin transporter -- there's its two different gene names; I usually just refer to it as HTT -- has been implicated in some way in liability to

autism, and I'll come back to that in just a minute.

A potential connection is that hyperserotonemia is common in autism. So there is some excitement about that. Now at the American Society of Human Genetics meetings, in fact, analyzing a new sample from AGRE, there is a kind of replication of the linkage signal on the chromosome 17 region, but it doesn't occur dead over top of the serotonin transporter anymore; it actually shifts slightly telomere. So that was interesting.

Unfortunately, Stone and her colleagues report that there's no association that they could detect at the serotonin transporter. So that kind of rules that out. But it doesn't really because this is a complex disease, and we don't totally understand what's going on.

Okay, hang with me for a minute because chromosome 17 gets even more interesting. If you look on the website for The American Journal of Human Genetics in the last month and you're just cruising through those studies, you'll see a study

of a quantitative trait locus for serotonin blood levels in the Heterites.

So they take these big pedigrees of Heterites and they analyze the serotonin blood levels, and, lo and behold, they actually show a gigantic linkage peak in the same region as the signals that are happening from the AGRE sample. Very intriguing, and they've actually been able to trace it right down to a particular gene which is an integrin beta 3 gene that is known to actually influence serotonin in blood levels. So there is a polymorphism in that gene, and they were actually able to show that, in fact, dysfunctional polymorphism explains the variability in serotonin blood levels.

The other interesting thing is that, in fact, it's sex-specific. It seems to be much more important in males than females. So maybe, just maybe, this integrin beta 3 is a key finding that's going to help us to link liability to autism. How it would do that I don't know.

Actually, there are other genes in that region that I find just as fascinating. That's why I said

to the folks in my group, okay, I want you to go analyze the AGRE data. We happen to have access to it. It's one of the wonderful things which got us interested in the whole area, having access to data. First, let's see what the signal is and then let's see if my theory is correct.

I'll tell you that my theory is incorrect, but we had some interesting results from analyzing the data. We tried to analyze the exact same data that was presented at the American Society of Human Genetics, but, clearly, we're not doing it quite the same way.

What we get is that, in fact, you still get a substantial linkage signal. If you look at the left axis, that's the NPL or linkage score, if you will; across the Y axis, linkage score; the X axis is the location in centimorgans. We do see a substantial linkage signal on chromosome 17 in exactly the same place that the other analysts for the AGRE sample see it.

What we don't see nearly as much is this amplification for male-only versus female-containing families. Male-only is in blue; female-

containing is in some other color that color-blind people can't see. Then the entire combined sample is in red.

So we do see some difference, but we don't see nearly the amplification that they saw in the male- only, and I haven't had a chance to get with the investigators and figure out what we're doing differently than what they're doing.

I will tell you that the analysis of complex disease is by its nature complex. We did some other analyses. We weighted families. See, if you look on the top there, in the caption it says, "Allegro Equal." What that means is we're weighting all the families equally. It doesn't matter how many affecteds they have in the family; we just weight them all equally.

Another way you might think about it is you should weight the families according to how many affecteds are in there, and you should give the families that are dense in affecteds more weight. If you do that, I don't have a picture of it, but it shifts the peak even more telomere, in fact, substantially telomere. It doesn't dampen it.

Something interesting is going on chromosome 17, but what it is we really don't know. As long as you're thinking about promising chromosome regions, and this is a region that's come up a couple of times this morning already, my favorite region is 15q11-13. I disagree that it's actually a linkage region. I disagree with Steve on that. There's almost no evidence that it's a linkage region. There's one study, I think, but, in fact, what's interesting about that region is it's the Prader Willi-Angelman Syndrome region. These two disorders come about by a failure for proper imprinting of particular genes in that region. So, as parents, when you transmit a gami from you to your child to make the fertilized egg, certain genes are turned on and turned off in the parents. This is called imprinting. What you see is that this imprinting region is oftentimes disrupted. I would say "often." Three to 4 percent has been detected in the autism families.

The other interesting side of it is that, if you look at Prader Willi patients and you try to characterize them in terms of autism behaviors,

they would look remarkably similar. So there's something extremely interesting about that.

The other interesting thing is, from my statistical point of view, that the sensitivity of the assessments to actually find things that are wrong in this particular 15q11 region is low.

Then we have a bunch of promising candidate genes. I thought I would bring you up to date on one of them. That' the serotonin transporter, which I'm going to show you some unpublished data from the CPEA along with all the other data that are published. So this is going to be a big table, and I'm going to focus your attention -- if I knew how to use this pointer, I would actually use the laser, but I'm going to focus your attention -- if I could actually see well enough, too, I would do it. Oh, this. Oh, good. Cool.

So I'm going to focus your attention. Here are the studies. In yellow are the studies that are different than the studies that are over here in whatever color that is.

What I'm going to focus you here is on the transmission of a polymorphism in the serotonin

transporter for the short long, which is known to be functional, I mean known to affect the expression of the gene. So these studies are ranked by their ratio of short to long transmission.

So the original study by Ed Cook and colleagues showed significant over-transmission of the short versus the long allele. In fact, they have the biggest ratio of short too long.

But the interesting thing about this is that, when you look down the spectrum of studies, you see some studies, the yellow, where there's significant over-transmission of the short, and then you look over here and there are three studies that have significant over-transmission of the long. This is particularly disturbing for people like me who like to think that there's order in the world.

If, in fact, this were having some impact on liability to autism, I would have expected, yes, there to be a number of studies where there was no significant over-transmission of short, but not significant over-transmission of long. That's a

very perplexing thing.

Now ignore the power for just a minute. I'll come back to that in just a second. So the other thing is let me just don my statistical hat for a minute and tell you that, think about it for a minute. We have only 12 studies in which there was reported transmission of alleles from parents to children, and seven of them are significant. That in itself is a noteworthy feature. Something weird is going on at the serotonin transporter locus.

It could be that the serotonin transporter, in these alleles are conferring liability to autism and they have an extremely small effect. If you did some estimation of what that effect is, you would come up, you would get four transmissions of short to every three transmissions of long, and even though it would have actually a big impact on population at attributable risk, the relative risk for this locus is not large at all. That's where that power comes in. In fact, none of these studies have good power to detect that particular thing.

What we will need, if, in fact, these alleles

have an impact on liability to autism, we're going to need huge samples. We'll need huge samples for linkage, even larger than what we would need for the association analysis that we have done here.

But really, if you think about it, I don't think this is a good candidate for autism liability. What I think it actually is, and what we have been speculating about in our group in the CPEA, is that what this is is a locus that, once you're liable to autism, once you're actually beginning to develop autism, it's going to drive how autism is expressed.

In fact, all the studies collect autism patients in slightly different ways. For instance, Nancy Minshew at the University of Pittsburgh collects only high-functioning autism individuals because she wants to study brain function in high-functioning individuals.

I think that's what is really driving this, is that we have a locus that actually has an impact on the presentation of autism and may explain some of the clinical heterogeneity.

Okay, let's move on. I'm going to just quickly

say there are plenty of under-investigated phenotypes for autism, and I wish that that would be cured. It sounds like the STAART Centers are actually making a good plan for actually filling those gaps.

The most under-investigated lead, as far as I'm concerned, are three little observations that I made -- actually, two of them I made many years ago and one recently, and then I actually want to comment on what Tom just presented earlier.

That is that it's true that the Prader Willi region is frequently disrupted in autism. About 4 percent is what we can detect. Another 5 percent, if you go through just a series of autistic individuals and you ask, are there gross chromosomal aberrations, 5 percent of them will have chromosomal breaks.

Now this new paper by Yu, et al., which appeared last year, showed that, in fact, when you study on a very microscopic level the chromosomes of autistic individuals, they find gaps that they don't find in unaffected individuals selected from the population. What's going on here?

Well, let me go back. To explain the 15q region, we have Art Beaudet's favorite hypothesis. Art is an expert on epigenetic phenomena. What he is arguing, very forcefully, at the American Society of Human Genetics meetings, I might add -- and I congratulate him for it -- is that geneticists are all wet; that this is an epigenetic phenomena, and that, in fact, we're going to find out that if we ignore epigenetic phenomena, we ignore it at our peril. I think he could be right. Again, all the data suggests that.

Art's data, however, when he does look for imprinting errors in the 15q region, it's pretty disappointing. He has maybe one or two cases out of forty that he can sort of ascribe to imprinting errors, but really he's not confident that they're imprinting errors, and I don't think we should be either.

So his favorite now is sort of a mixed genetic and epigenetic hypothesis to cure autism. Mine is, too, but it's slightly different. I'm going to give you mine now.

My hypothesis is that it is a mixed genetic

mechanism in two generations; that, in fact, we're seeing an awful lot of chromosomal instability in autism, and we have to think about that. There's something to that potentially. That's what I have been focused on for the last couple of years, but it's actually a hard nut to crack.

Putting all those data together that I talk about and then putting on my statistical hat, you know, the sensitivity of detection for these kinds of chromosomal aberrations is actually quite low. That, to my mathematical mind, says, heck, the number of chromosomal abnormalities in chromosome 15q has to be larger than that. The number of non-chromosomal 15 abnormalities has to be larger than what we've detected so far. In fact, those micro-deletions have to be a lot large than what we saw.

I was surprised by the Yu paper that they didn't actually go into that in the mathematics. So then the question becomes, well, who's affected for autism? I think that's something you need to think about. Who's affected for autism?

Certainly, the children are affected with autism, but could it be that the parents actually

have some also alteration which affects the fidelity by which chromosomes are transmitted between generations? That could be an alteration in the genetic level or it could be an alteration at the environmental level, but that's what the data tell me, that you'd better look carefully at that.

Unfortunately, you're not going to get at that from linkage studies, and you're not going to get at that from transmission studies. But I'll add a positive note in just a minute.

So this is the important thing: I'm not necessarily right. Art Beaudet's not necessarily right. The pure genetics hypotheses are not necessarily right. I think we have good, promising leads for the genetic hypothesis. There are gaps with respect to phenotypes which now I hear are being filled, and that's fantastic.

There is some promising evidence for this mixed epigenetic and genetic hypothesis, but there are gaps in that, too. There are gaps for my hypothesis of mixed generational problems. But the interesting thing is studies are underway for all

of them.

What if we're all partially right? If we're all partially right, there are two consequences. No. 1, as Art argues, you ignore those hypotheses at your peril. If there's a strictly genetic analysis of the data, focusing on the affected individuals in that generation, you might be overwhelmed by etiologic heterogeneity. You may see no linkage signals. That's a big thing that I'm quite nervous about as we head into the NAAR study.

At the same time, if you take those hypotheses and you meld them, and you look at them, we might actually make some serious headway. So the reasons for optimism are plenty.

The reason that there are so many resources coming into the field of autism right now is that the resources have been made available from NIMH, from AGRE, via CAN, and other resources. Tremendous resources are what brought me into the area, because I thought, well, you know, I have this wacky idea, but what can I do about it? But then all of a sudden I knew, oh, the AGRE sample

is there. Well, I can actually begin to test that idea. It hasn't been easy, but I have some interesting leads.

What's being fostered is a competition. As more good people flow into the area, the people who have been there for a while, everybody's mind gets focused.

Now I hear a lot about collaboration or cooperation, and I think that's very good, but in the scientific area it takes cooperation and competition because people's minds really focus when you have competition. I think competition is great.

Hypotheses are flowering, and I think that, as I said, I could be foolish, but I think there's real reason to be optimistic that we're going to have some real insights into the genetic and environmental basis of autism in the near future. Thank you.

[Applause]

Questions?

Dr. Gordon: A question.

Dr. Devlin: Good.

Dr. Gordon: When you list your plausible hypotheses, can you estimate an end that you need to test them with reasonable power? I mean it seems to me, looking at your data, that the samples you've had so far have generated a number of working hypotheses, but nobody has the power to quite test them, especially as you get into more and more plausible possibilities, such as heterogeneity, multiple factors, epigenetic and genetic, and so forth.

So if you listed some reasonable hypotheses, what would be the true "N" required to test that, to give you a reasonable power? Is it beyond conceivably any current cooperation? Would it take examining the population of a small country or a large country?

[Laughter]

Dr. Devlin: I mean that's a good tough question. The answer is, of course, I'm uncertain. I don't want to look too foolish. But, at the same time, if we have gene/gene interaction -- I do believe we have a substantial gene/gene interaction. I do believe we have a pretty good

shot with 1300 families, which is what's being put together for the international collaboration by NAAR. I think we have a good shot, but I'm not overly optimistic about it.

We don't have the right sample to look at this hypothesis that I just put forth, that there are some genetic alterations in the parental generation; that in the mechanisms that check the fidelity of chromosomes, we don't have the right sample. That doesn't mean that we can't do anything.

I've been trying to do analyses for years, and what's going to be extremely interesting is, once these data are available, even though it's not the right sample -- in fact, you know, the right sample would be much more extended pedigrees, so that I can actually look at the transmission of alleles not just from the parents to the children, but from the parents to the parents to their children, to the parents of the children. So that would be the ideal pedigree configuration.

What we have been doing instead is we've been looking at these ideas of whole gene association

on the parents. It's yielded some interesting results, but nothing that I have wanted to publish because I just can't interpret it.

Dr. Insel: I'm going to try to back up Bernie's comments here because I think, Barry, you're asking a tough question and there are two ways to think about it. One is to look at what's happening in other areas of medicine. So for the type II diabetes community, they decided their target was somewhere over 10,000. Actually, it was when they hit 8,000 to 10,000 that they started to find genes through these same kinds of approaches. So we're pretty shy of that.

But I think what Bernie is suggesting is actually much more interesting, that maybe, if you decide that the problem here is around issues like chromosome instability, and then it actually takes you down a different path. Then you're not concerned so much about finding thousands of families. What you really want then is an intensive study with some new approaches in very well-defined populations.

I think it's a place that we haven't actually

discussed. We haven't talked enough about this, because if you look at the literature, for instance, on cytogenetics and autism, it kind of ended in the eighties or nineties. There's not that much written in that area.

There's a funny place where this is kind of coming back to us. You wouldn't expect this, but it's in the field of comparative genomics, where when people like Eric Green, who's here in NHGRI, have looked at differences between the human and chimpanzee genomes, what they find is that most of the difference is in constrained areas.

Some very recent work by Evan Eichler, who's now at the University of Washington, has given us, I think, a great opportunity to focus in on this. He discovered that in the genome there are about 128 areas across all 3 billion bases where you've got a segment of a hundred or more bases that are highly homologous to the opposite strand, but offset by about a hundred bases. So what that means is those are areas of instability. Those are areas where you get this recombination at a very high likelihood.

Evan went through; he identified all 128 areas, and it turns out that many of them actually fall right on top of currently known disease-producing genes or alleles that are important for vulnerability. Now not all of that has been explored. But you could imagine taking an approach like that that wouldn't be so numbers intensive and really focusing down on specific hypotheses and specific genes that live in those areas. Some people are beginning to think that way.

So I think it goes back to your first slide. Maybe we could be a lot smarter and a lot less certain about our approaches at this point and think about whether some of what's cure is not actually going to come out of the linkage or out of association studies in a classic sense, just some thoughts.

Jose?

Dr. Cordero: I think that the topic of do we have enough sample size is a recurrent theme, and I'm glad that Barry brought it up. I would like to sort of step back and look at data on what the rate of autism is, and if we take the conservative

of two per thousand, that comes to about 8,000 children in each year, each cohort, with autism. If we take perhaps the highest end of six per thousand or 166, that comes out to about 24,000 cases of autism.

And, yes, even considering that we're really dealing with a spectrum and we have different types of autism, that still is a substantive number, and that efforts in terms of early identification can actually be linked to, then be able to connect to the studies that need to be done, whether they are novel studies, linkage, or others.

Dr. Gant: Hi. I would like to look at the elephant from the other point of view, which is I think the concept of sort of the basis is instability is interesting, but the interesting part is the instability in certain areas seems to lead consistently or so-so to autism.

Has anybody backed down even to the level -- since biomarkers are a huge issue in heterogeneity and studying this disease for treatment, does anybody here know that someone's taken the cohort

of kids who actually responded to SSRIs and evaluated them specifically for genetic disturbances in this area, perhaps related to serotonin transporters? Because if you can carve out a subset from the therapeutic point of view to study, there may be some value in that. Has anybody done that?

Dr. Insel: Well, that's been done in a major way in depression, and it's been only partially successful. It's actually been more useful to use that approach to identify who's going to have adverse events in response to the drug than find out who's going to respond.

But there' a big effort in that, and, of course, the numbers are huge because we've already got very large studies underway in pharmacogenomics. Autism is going to be such a small segment; you won't be able to generate the power, I don't think.

Bernie may have a better sense of that.

Dr. Devlin: No, I agree with you 100 percent and not that I know of in that particular setting. I wanted to actually echo something that Tom said,

which is that, you know, once we have these ideas out there, you can actually do focused studies. What we need are people who actually understand the epigenetic phenomena better, like Art Beaudet, and we need people not like Bernie Devlin, but somebody who actually understands chromosomal instability. I'm a statistician; what do I know about it?

But, I mean, I look at these signals on the chromosome and I think there's a lot of them; I don't understand them. But maybe somebody who does will actually be able to drill down on that very quickly. I think that's where it's going to go. I think that's where we're going to get some breaks.

Dr. Insel: Yes, thank you very much. I think a lot of things are breaking right now. The current issue of Nature has an extraordinary paper which may be also the vision of the future for this field. It shows that there are areas what are called now microprocessor RNAs. One of the areas that popped out is the area on chromosome 22q, which is the VFCS, the place that's associated with a very high rate of schizophrenia in the

children who have velocardiofacial syndrome.

Just like in autism, we haven't been able to figure out where the genes are in that whole segment. It's a micro-deletion just like the story where we know there's a high association with schizophrenia in children, but none of the genes in there seem to be the key gene that causes the disease.

Now it turns out that in this very same spot there's a small RNA fragment that's called a microprocessor that makes something that goes out into the cell and sort of tags onto lots of different proteins. Who would have thought? We didn't even know to look for this up until a few months ago.

So it could be a very important kind of lead and a new way of thinking about how either instability or how small areas that are not often associated with classic genes can be very much involved. So I think we have to get a lot smarter before we just worry about getting bigger.

Okay, on that note, speaking of getting bigger, why don't we break for lunch? Can we plan

to get back at 1:30? So we'll have a slightly shorter lunch break, and we'll get started for the afternoon session then.

[Whereupon, the foregoing matter went off the record for lunch at 12:34 p.m. and went back on the record at 1:35 p.m.]

Dr. Insel: Let's get started with the afternoon session. And we're getting started with services and, as we would like to say, NIH from science to service. The report from the Services Subcommittee will be led by Dr. Merle McPherson from HRSA.

Dr. McPherson: Good afternoon. I am simply going to make a few introductory remarks and turn it to a panel of people from our expert workgroup, who will talk through for you the presentation this afternoon.

I guess I am feeling a little bit odd and overwhelmed having had the science of the morning given to us and having to come back and take it back down to the service level and children and families.

Sue and I were out talking. And we were saying

how valuable it was, this committee, where the service people did sit and listen to all of the research and heard what was going on. We also, therefore, talk back to you in terms of what the service system needed to be. And through that, I hope we can really develop some real opportunities to translate that wonderful science we're hearing about into practice and look forward to working on those issues.

We are obviously very pleased to have the opportunity to present a status report on our efforts to create a services road map, which is modeled on the work that was done to create the research road map. And we are close to completion of a final draft. This is a status report, however.

Sybil Gowan and I with the support of Anne Wagner and Audrey Thurm from the full committee have chaired a subcommittee that is made up of consumers and the major agencies in DHHS and Education.

And I think that is terribly important to know that we have a subcommittee of all of the

government agencies in HHS and Education who are concerned and have some level of responsibility for the systems and services for persons with disabilities and special health care needs. And so we are working across agencies.

The subcommittee invited a broad-based expert workgroup to develop the national road map for service delivery and systems building, which is going to be described to you today by three members of that workshop. It has been an outstanding expert workgroup. They have worked very hard in getting this report together. And I think you will enjoy it.

Before they do that, I only want to comment on three points. One, I want to acknowledge the complexity of services in this country for all people and for all people with disabilities.

We all know and understand that it is a very complicated delivery system that is made up of public, private, and voluntary activities. The public programs come from multiple agencies at the federal level, the state level, and the local agencies. And certainly that public-private-

voluntary partnership is incredibly important if we are to succeed in getting the pieces of the puzzle put together so that services really are available in some kind of an organized way for persons with autism.

And it's, therefore, because of the complexity of the service system and the imperfect nature of it at this point in time because it is not universal and sustained and equitable across all people, it is incredibly challenging to take one condition and talk about how you begin to embed the specificity of services that we need for persons with autism into that service system.

Therefore, the second point is the importance of full inclusion for persons with autism in programs for all children, youth, and families and into systems of programs for disability. We decided this could not be a lonely highway separate from the main roads. And I think that we are really pushing for full inclusion.

Finally, because of that, we have agreed to develop in the context of the President's Freedom Initiative. Many of you here know and under the

President's Freedom Initiative. It was in response to a Supreme Court decision that called for community options for all persons for disabilities. What it essentially said was that you could not simply insist that people go to institutions because you did not have community options available.

So that out of that, the President created what is called a New Freedom Initiative with a report delivered in March of 2002. And it was a report, a compilation of reports, by nine federal departments, including HHS, Education, but also Justice, Labor, Housing, et cetera, into a report that talked about the barriers that needed to be removed from government to permit community living for all people with disabilities.

Within that Freedom Initiative, there was a charge to develop and implement a plan that achieved community-based systems of services for children and youth with special needs and their families. And our Social Security legislation also requires that.

There is, therefore, partial implementation in

every state of the attempt to put a community system services in place. And with this workgroup, we have expanded it beyond for the full life span. So we're talking not just about children and youth but also the adult population.

Therefore, I am going to turn to the panel, who are going to talk to you about the plan that is embedded in the President's Freedom Initiative.

We have three people. I have told them that I would not waste their times by reading their biographies, which are long, and that their words will speak for themselves.

Right comes David Mandell, who is Department of Psychiatry and Pediatrics at the University of Pennsylvania School of Medicine Center for Health Policy, Mental Health Policy, and Services Research. David actually has spoken to us before.

Cathy Pratt is then going to follow up from the Indiana Institute for Disability and Communities at Indiana University. And I think anybody who is engaged with the world of autism knows Cathy.

And the third is Stuart Spielman, who happens

to be a lawyer but, perhaps more importantly here today, is the father of a child with autism and is on the Board of Community Service for Autistic Adults and Children in Potomac, Maryland.

I'm going to turn this over to the panel. And we have agreed we will leave some time for questions and discussions after they're finished.

David, do you want to take it?

Dr. Mandell: Thank you, Merle. I also was excited by the research that was presented this morning and was struck by the words not of Bertram Russell but of Monty Python, who said, "Now for something completely different." But, then, in thinking about it, it's not really that different.

And what we're really talking about is a continuum. That is, when someone in this room develops the treatment that is effective for autism, how are we going to disseminate it? And how are we going to make sure that there are providers who have the capacity to provide it? And how are we going to make sure that there is a system in place to pay for it?

Those are the types of questions that we try

to address on this panel. It was a wonderful group that spent the last -- still is a wonderful group that spent the last several months sharing expertise on the service needs of individuals with autism.

For this presentation, I am going to give some background on the problem and our process. Cathy is going to talk about the current challenges and our recommendations regarding family-professional partnerships, screening, and access to and coordination of services. And then Stuart will discuss issues of helping adults with autism lead independent, fulfilling lives and challenges regarding service financing. He is also going to present a summary of our recommendations and our next steps.

This group, which included people with autism, their parents, not only the parents of the people who are there but other parents of people with autism, providers, researchers, and administrators, representing a variety of different perspectives and experiences. It has been an exciting and frustrating two days together

in the bowels of a D.C. hotel.

It is a wonderful group of thoughtful and experienced people dedicating to improving services for people with autism. The process has its frustrations, however, because of the paucity of related research and the lack of dissemination of promising practices. While we all drew from our personal experiences, there was not really a body of literature as much for us to draw from.

These are the people, by the way, who comprise the expert working group. I want to talk a little bit about the scope of the problem. This slide represents data taken from the U.S. Department of Education Web site, speaking about data sharing, and represents the number of children in the United States, ages 6 through 21, who are in the autism category of special education.

You can see that number over the last decade has quintupled. The percentages above each bar represent the percentage that children of autism comprise of the entire special education population.

So you can see that they are a growing

component of who the special education system is serving. Of course, this slide leaves out even the faster growing number of children ages three to five diagnosed with autism as well as children with autism who are misdiagnosed.

And I hesitate to quote a study whose authors are sitting in this room, but I believe that the CDC study in Atlanta found that 18 percent of the people in their study ultimately diagnosed with autism were served by some other special education category.

This traumatic increase has caused a crisis in the communities in which these children are identified. We all know that autism is a chronic condition with no known cure that presents with polymorphous phenotypes and with varying degrees of severity.

Recent research has greatly improved our ability to identify children with autism early. We have been less successful in creating a system in which those intervention needs are met in a consistent and sustained manner.

Some treatments have been manualized but not

disseminated. There are no published guidelines for the types and intensities of services people with autism should receive.

Many, if not most, professionals from primary care doctors through development specialists do not know what treatments and service options are or should be available to people with autism. Even if they do know and even when those services are available, the state of public and private financing for those services in the United States is in disarray, making some services effectively unavailable or prohibitively expensive.

Our intention in this report is to begin to suggest a national plan for the organization, delivery, and financing of services to individuals with autism. Our goal throughout this process was to develop a plan that was based on existing systems that expanded services for individuals with autism and that proposed mechanisms for coordinating those services across the multiple systems in which individuals with autism can or should receive care.

So this is where we started. More specifically

our starting premises was that there is an urgent need to improve the current care system and that existing mechanisms at the federal level and current programs for individuals with special needs offer a framework for that improvement. We based our thinking in our report on the six constructs from the President's New Freedom Commission on Mental Health report.

Within that context, we tried to address issues across the continuum of service organization financing and delivery. This included the continuum of service providers from primary care through autism specialty care. It included the continuum of service types, from those that affect everyone, like screening, to those that affect children with special health care needs, like special education and respite services, to those that are specific to individuals with autism, like certain treatment strategies or sources for autism-specific information and advocacy. It also included the continuum of entities that fund these services, including the family, private insurance and public programs,

such as Medicaid and special education funding.

Cathy and Stuart are now going to present the body of our report. I wanted to present the six issues from the New Freedom Commission that provides our outline.

We discussed family, professional partnerships early in continuous screening, access to all necessary services, mental health, health, education, and social, community-based, coordinated service systems, transition to adult services, work in independence, and adequate public-private insurance and financing.

Dr. Pratt: I was reminded as I was involved in the work of this Committee that, first of all, you need to know that I have been in the field of autism for about 30 years. This is the point at where my staff usually says, "And she began at the age of five," a comment that I always appreciate from them.

David made the comment during one of our phone calls that he was young and highly anxious and highly motivated and impatient to see change happen. So I just want to add that I am old and

impatient to see change happen.

I am also reminded of the fact a couple of weeks ago I had the opportunity to be at the AUCD conference because the institute that I work with is part of the Association for University Centers on Disabilities.

Just to again encourage that, the AUCD as I was listening to all of the speakers, the issues are very similar across disability categories. We're really talking about creating systems and services that work for all individuals.

I am reminded of the analogy that when we looked at creating wider stalls and when we created curb cuts and those things on behalf of people with disabilities, what we really were talking about was an accessibility issue. And what we are really talking about is an accessibility issue for families and professionals and for individuals on the autism spectrum.

This issue is also near and dear to my heart because as Vice Chair of the Autism Society of America, the Autism Society of America has been very dedicated towards services and making sure

that as families and individuals seek employment opportunities and as they seek opportunities in schools and as they seek access to medical care and other kinds of services, that we can do all that we can to advocate on behalf of improving those services and those options on behalf of individuals with families.

So I am proud to be involved with that organization and their continued focus on making sure that people who are living in the here and now are dealing with this disability and have the resources and services to be able to do so.

And now I will be computer-impaired. Okay. These are the goals that we came up with. And, again, let me just also voice that it was a wonderful group of folks to meet with.

We realize that these goals are ambitious. These are goals that I have been hearing for a while. And so the importance of them is not to be underestimated. And I think all three of us are so interested in now what do we do?

The first goal is that all individuals with ASD in their families will have a well-respected,

trusting, and mutually respectful relationship with a health care professional who listens and responds to concerns and acts as an equal partner in providing a clearly defined plan of coordinated services.

One of the themes that we heard from the family members on the panel was that they often felt that when they went to their medical professionals or other professionals, that their ideas were somehow diminished, they weren't taken as seriously. And so there needs to be that partnership.

I always resist and I hate the comment when people call me and refer to me as an expert in autism. I don't live with autism. I don't have a child with autism. Families who are living this every day are those who have the expertise, who understand what it is like to live on an ongoing basis. And there does have to be a partnership.

The other thing that is really important in this -- and this is a theme that you are going to hear throughout these various goals -- is this concept of coordinated services.

One of the other comments that we heard from several of the family members was that we have silos of services. As families move from one silo to the next, what you find are different funding mechanisms. You find different rules, different regulations, and different ways of accessing that.

And so it is a theme that you are going to see reoccurring throughout these slides, but getting away from those silos was a really important issue for families.

So as we look at the family-professional partnerships, again, a lot of these are going to be very similar: lack of time, knowledge, support, and training. Again, families will tell us that when they interact with various professionals, that there is a lot of misinformation that is still out there about what autism is.

Not too long ago I had the opportunity to spend some time with a little boy with autism. His parents made the comment that in his community, the professional, the physician, didn't believe that the child had autism because he liked to be hugged. Well, he liked to be hugged because he

loved deep pressure. But that misunderstanding really led to a mislabeling. And we see lots of stories of that, lack of understanding and communication regarding ASD and, then again, the failure to integrate multiple systems serving individuals with ASD, again the theme of the silos.

So as we were talking about some of the recommendations, training is going to be another recommendation that you see throughout providing ongoing training and technical assistance for professionals and families to engage in full partners because I think part of this is also that we have to make sure that families really understand how to engage professionals.

I think the other thing that is very different about the services report than is a research report is for those of us who are in the trenches and dealing with the services around these individuals, I know as Director of the Indiana Resource Center for Autism, I have to make sure my job and something that I take very seriously is that every individual in the State of Indiana has

equal access to services, regardless of their socioeconomic status, their racial, their ethnic, their cultural background. Okay?

And that is a real challenge because that means that we have to look more broadly and not just look at creating centers that people have to go to but how do we actually get into the field and make change happen for those individuals who maybe are living below poverty level. And that really is a challenge for us.

So increase ASD information and education resources capacity at the national and local level. And you will also see a theme throughout here where we talk about not only just at the national level but that we need to get down to the local level because that really is where change happens. That's really where the rubber hits the road.

When a family member has a child who is diagnosed, I know for me in Indiana, what I find is that families will start, first of all, go on to the Web and find the Autism Society of America.

But the other thing that they will do is start

connecting with people in their community, with the professionals in their community. And so we have to take it down to the local level and then integrate ASD into existing initiatives to strengthen family support and involvement and to establish that integrated system of care, again getting involved with other systems.

Next is that there is universal practice of early identification of signs of ASD followed by appropriate referrals to a coordinated and comprehensive service system, again that idea of coordinated and comprehensive service system.

What you will find is if you travel around this country, -- I know I hear this from a lot of families -- depending on where you live makes a difference as to the types of services that you receive. And families in certain areas have just tremendous resources and tremendous services. And then they may jump across to another state or into another community or into another neighborhood. And what they see is very different than where they came from, so having some more consistency.

Again, the challenge is lack of awareness,

time, training, and reimbursement. One of the concerns here was the fact that to look at doing screening as part of just a regular checkup, right now physicians are not being reimbursed for children to be there for a more complete screening in that there needs to be some changing in that so that there is a more comprehensive screening.

Inadequate screening and diagnosis methodology and capability. I get a lot of questions about what are the tools, how do we tell, what are the screening instructions. And then, again, inadequate linkage to the referral resources and service network.

One of the things that we batted around was this concept of having actually kind of a Web site or having some information that families can go to to find out about the resources in that area.

The Autism Society of America has started such a resource and referral system but really making sure that families have access to those kinds of things and that they know what is available in their community.

Our recommendations were to support what is

happening with the Screening Subcommittee and their efforts to increase public awareness and to incorporate ASD into routine screening, develop guidelines for ASD screening and diagnosis so, again, that there can be more consistency about what happens, to incorporate ASD guidelines into curriculum for residency, professional certification, other training.

I know one of the things that I and my colleagues have been doing in the State of Indiana is to actually go and do rounds with physicians and talk to them about characteristics.

What we find, at least in Indiana, is that a lot of our physicians maybe have one lecture that is dedicated to children on the autism spectrum. And if you look at the numbers, you can see that the reality of it is that physicians will be seeing children on the autism spectrum in their office. So that one course is not really very sufficient or that one lecture is not very sufficient to make change happen.

And, again, promote linkages between primary providers and existing networks for developmental

education, rehabilitative, social, and specialty services for ASD.

What happens right now is that when families receive a diagnosis, they end up kind of shopping around. Let me just tell you the scenario of how it happens in my state. I would like to think that we really make an effort to try to give people information about how to connect with services.

What happens in our state is that a parent finds out that they have a diagnosis of autism. And if they're lucky, they go to one of our teaching or research hospitals that hands them a packet this big of information.

And they're already overwhelmed with the diagnosis. And so once they deal with that packet and they go through looking at all of the information on the Web sites, they may find because of some connection another individual, family member, who has a child, a son or daughter, on the autism spectrum.

And then what they do is that they spend a lot of time with that person trying to figure out, who is it that I call, who does what. Word of mouth

becomes the resource.

And that's really great for parents who are able to find that person who can kind of tell them about the services, but also too often we find families who are so intimidated by the process that they are not able to figure out what those resources and services are and to get linked to them.

The next one is that individuals and families with ASD have ready access to integrated and coordinated health, mental health, education, and social services provided by well-qualified ASD providers throughout the life cycle.

The challenges aren't lack of providers. And one of the things that I do in my free time is that I serve on the board of directors for a group home organization in my community. It is a group home organization that was actually founded by parents of children on the autism spectrum and has continued to expand their services. And now as we are moving people out of state institutions or state developmental centers, we are taking on some of the most difficult and complex folks.

One of the challenges that we find is the ability to find providers who are qualified to do that. Our group homes have had a tremendously difficult time finding physicians who will address and handle the medication needs of individuals in our group homes, who will deal with the counseling and psychiatric needs of individuals with autism.

See, in the 30 years since I have been involved in this profession, not only have I gotten older, but the fact of autism has changed. And where autism used to be a diagnosis where individuals were more similar than different, what we see is individuals coming to us who have complex needs, tremendously complex needs, that not only require us to look at educational and work and living support but also for some of our individuals to also look at medical assistance because we are starting to understand the biological basis of autism and also needing some psychiatric support because we know that, in addition to having a diagnosis on the autism spectrum, some of our folks also have psychiatric conditions, such as anxiety disorders and

obsessive-compulsive disorders. So as these individuals that we're seeing become much more complex, it becomes much more complex to figure out who exactly folks go to.

I get a lot of phone calls from people all over the country who are trying to find services for their loved ones in communities.

Inadequate time resources and reimbursement. The other issue that I see in a lot of our direct care providers is that our direct care providers who work in employment situations and who work in residential situations are incredibly unpaid. And, quite honestly, they could work at McDonald's for better benefits. They stay in those jobs because of the love that they have for what they do.

But what you will see in those organizations, those direct care organizations, is an incredible turnover of providers. And what that means for families is that they never know when they walk through the door who will be helping, who will be supporting, who will be there with their loved ones. And that inconsistency of programming is terrible.

One of the things that we look at is -- I know in the group home organization that I am involved with and supported living organization that I am involved with, one of the things that we have grappled with is, how can we reimburse people so that they are more committed to stay? How do we train them? How do we invest in them to help them understand the valuable service that they do? Because when we don't invest in them, we don't give them a good message about the value of their work.

Also, lack of education, training, and support for families and multi-disciplinary professionals. As we looked at this, you know, we weren't talking about -- I didn't hear from any of us -- and, Merle, please, or Stuart or David -- I didn't hear from any of us talking about creating different systems for doing any of this, for any of the training.

One of the systems that I looked at was the AUCD network that Lou Zephra is part of because that network, our mission as part of that network, is to do training, is to do national training.

That's what we do. And so using existing resources to all of the various autism organizations use those existing organizations to make a difference and then again a lack of services and coordination across existing services and again the concept of silos.

So the recommendations were to develop ASD practice guidelines to define standards of care. How do we know in these direct service agencies that people are doing the kind of jobs? What are the quality indicators? How do we know that we are producing the kinds of outcomes that we hope to achieve?

See, I was a classroom teacher for a lot of years. And I had a very simple way of judging the outcome of what I was doing. The way that I judged the outcome of my job was not whether my students met their IEP goals, although I thought that was incredibly important.

How I judged the outcomes of what I did was if I ran into one of my students when they were 25 or 30, did they have a job and were they living in the community, and were they being successful?

That is really what I focused on.

And I think having some practice guidelines that get us to those outcomes is incredibly important.

Again, incorporate ASD service guidelines into curriculum for residency, professional certification, and pre and in-service training. Both in education and in the adult services, a lot of our direct service providers are not trained. Hire professionals in schools.

And the people who provide direct service oftentimes get no training other than to say, "Here are the files. Here is the refrigerator. Here are the forms you have to fill out to get paid. Have a good day."

I think this is an issue. Pat, I am looking at you because I think this is an issue for all of our folks with disabilities, that we oftentimes put folks who are sometimes very vulnerable in the hands of those people who do not have a lot of training and support in whom we have not invested very well, so making sure, again, that we do that.

Again, provide incentives to ensure greater

availability of well-trained providers and a more equitable distribution of services across geographic areas. Again, we have to be concerned that we are covering every part of this country and that if somebody moves from Minnesota to California, that they can be ensured some of the same quality of care, some of the same standards of care, and that we would develop an action plan for collaboration at all levels to address the service needs of persons with ASD within the broader initiatives to develop community-based systems of services for all persons with disabilities.

One of the things that I talked about when we met as a working group -- and, Gail, the Department of Education has done a wonderful job of this. They have developed a system of state improvement grants in education. And what happens with those state improvement grants is that key players in the state get together on behalf of education. And the focus of those efforts, of those initiatives is really on transition, making sure that students are meeting academic standards,

early intervention, a whole host of things.

But the idea behind that and how it is working in my state is that it has pulled together all of the key players to say, "How do we from the various organizations come together to meet these goals?"

One of the other things that as we looked at, as we talked about what was going on in this country, one of the concerns that we had -- and, you know, Stuart and I talk every once in a while. We run into each other in meetings. And so we are kind of aware of what is happening in each other's states.

There is no mechanism for all of us to get together from states to say, "You know what? Guess what we're doing in California that is really working well."

Well, what has happened with the state improvement grant is that it provides a venue for those project directors to get together and share information about "Here is what is working in all of our states" because I really believe that in every one of our states, there is incredibly good

stuff going on, there is incredibly bad stuff going on. And how do we share those models of excellence to make sure that we're able to replicate those across different areas

The fourth one is that community-based services will be organized so that individuals with ASD and their families can use them easily. Again, these are some of the consistent themes: ineffective integration of ASD services into broader systems of care, again not looking at creating a separate system but how do we make sure that the needs of folks with ASD are included into those broader systems of care?

My job is — the job that I get paid for, is as Director of the Indiana Resource Center for Autism. When I go into a school, I am called into a school oftentimes because of the behavior of the child on the autism spectrum.

It is very clear as I go into those schools that a lot of my job is also about how do we create a different culture in schools that is not only more supportive for students on the autism spectrum but is more supportive of all students,

both students with and without disabilities. And that's really what we were talking about. And that diagram really illustrates this. How do we create those systems?

Lack of interagency coordination, again the silo idea, lack of access to information, and lack of time resources and reimbursement. And the recommendation is to support family-driven. And family-driven was always an important component I hope that you say throughout these recommendations that we make sure that these are family-driven and individual-driven and that we look at community development initiatives because, again, we're not really interested in creating kind of national levels of services. What we're really talking about is how do we get into the community? How do we make a difference where people live?

Provide technical assistance to states and communities to implement effective service delivery models so that those places that are doing things that are just excellent, we can replicate those in other areas.

One of the things that families talked about -

- and this goes along with the next bullet -- is that as families go -- and, again, let me use the State of Indiana as an example.

When families have a child who is diagnosed, in our state, what happens is that your child in between the ages of zero up to three gets involved in a program called First Steps.

Then from First Steps, they go on to education and through elementary and middle school and high school. And then depending on their career track, they either go on to some post-secondary job or they go on to voc. rehab or some other adult services.

One of the things that again happens in our state is that the rules and regulations change. For example, even within the school system, when you move up to the age of about 14, then you have to start thinking about transition planning.

For families, what we heard from the families who are part of this committee is that it would be nice to have an individualized plan that was a coordinated plan that talked about how we bring all of these service systems together and how the

families would be able to kind of jump across those service systems and how they would be facilitated.

Ideally one of the things that was brought up is it would be nice to have a point person kind of lead them through all of those steps because it does become very confusing and overwhelming.

And then identify and analyze effective models. Find out those places in this country that are doing a great job and figure out what it takes to replicate them.

Mr. Spielman: Okay. Well, I'm very pleased to be here. I think my principal qualification is that I am the parent of a ten-year-old son with autism. So this has given me some in-depth experience with the system.

I'm going to speak first about transition to adult services work and independence. The goal here is that all individuals with autism spectrum disorder will receive the services necessary to make transitions to all aspects of adult life, including adult health care, work, and independence.

What strikes me about my particular situation and how it's relevant to this is that my ten-year-old son is starting to get to the point where I think people will no longer regard him as cute and cuddly and all of those nice things. And he is going to require adult services.

Now, as a child, he has received a significant amount of services, but what happens when we cross the bridge and he starts engaging in not-so-cute behaviors as an adult?

Some of the challenges that we face here in the transition to adult services, work, and independence is the lack of information about current services and experience of adults with autism spectrum disorder.

I don't think that we really know a whole lot about the adult population. It's a remarkable thing that when we talk about autism, when we talk about autism research, we generally focus on children.

When we talk about early intervention, we talk about the services to children. But I haven't heard about later intervention. I really have

heard very little bit about program, research into programs for services for adolescents and for adults.

I was motivated to go through the research matrix. And, sure enough, there was something there in the research matrix about providing services to older people; that is, non-children. The matrix notes that there is a real need for real world research understanding of what happens after kids cross the threshold and become adults.

I think our group would echo the call that we need a great deal more information about what happens to adults. If we're going to address the needs of this population, we need to know a lot more about them.

What do we know about young people and adults with autism? Well, we know that there is lack of appropriate education and training, families, professionals, and communities. Cathy mentioned this. There are just not a lot of services out there. And families are always fighting to get those services, find out about those services. The information about those services is often lacking.

We know that there is ineffective transition planning and coordination of services. In some instances, there is no transition planning. It's just what there is often haphazard and doesn't produce the results that we would like, a few services tailored to adolescents and adults.

I can recall a conversation I had with a young adult with autism who was working with my son in a physical education program, trying to help Zack keep in shape, which is difficult for kids with autism to do. And he told me that one of the great difficulties in his life was that as an adult with autism he had tremendous difficulty meeting people. And he didn't know how to go about doing that. He was looking for some assistance.

I'm president of the board of directors of Community Services for Adults and Children, which is a large service provider in Maryland, I thought. We don't really offer any assistance in that. And I don't know who offers social groups, meeting groups for adults with autism, which is another indication that when you age out of childhood, you basically fall off the planet, few

services and no entitlement available for adults with autism spectrum disorder.

We have IDEA, which is a mandate for services for young children, but what do we have for adults? We have Medicaid programs, but not everybody is covered by those Medicaid programs. Some people are not covered by those Medicaid program. What services is that population getting?

So what are our recommendations? We recommend collecting data about the life experiences in these adults with autism spectrum disorder so that we can begin to address these issues. We recommend starting early transition planning.

We recommend development and support of skill-building opportunities that promote self-determination in youth with autism spectrum disorder. We also recommend providing an array of services and supports in the community. Much more needs to be done in the community.

Aging issues have to be addressed. And we have to deal with issues like estate planning. I get the sense from talking to other families that they really have only a vague idea of what is going to

happen down the road to their kids as they grow up.

The whole concept of a geriatric autism population I think is a new idea. I know that in CSAC, this is something that we are beginning to grapple with, that we're going to have to provide services not only to an autistic population but to a geriatric autistic population. And when I've spoken with people at CSAC about that issue, they kind of shrug and say, "We don't know where to go on this, what models are out there, how much information is out there about that population."

We also think that it is important, we as an expert working group, to formalize partnerships, ensure collaboration across service sectors in providing transition planning.

And, finally, it's important that we put together a task force that identifies the needs of adults with autism spectrum disorder and how to address those needs.

I am still fortunate that my son is young enough for me to look at him as a child. And I like to look at him as a child. But, you know,

that's just sort of an indulgence on my part because he will be an adult. And he will need services that I can't provide for him or that I may not be around to provide for him.

Let me go to the next slide if I can go forward and not backwards again. I keep on going backward. That's a bad sign. I don't know how to do this. I guess that's a good sign for me.

All right, this is an area where maybe I had some professional credentials that help me to speak a little bit on. That's the area of public and private insurance and financing.

The goal here is to expand public and private financing of autism spectrum-related services so that individuals with autism spectrum disorder and their families have access to early and continuous screening, comprehensive diagnosis, and health, mental health, education, and social services, a long, long sentence.

I'm a tax lawyer by profession. I don't think that too many tax lawyers wind up in this place. I haven't seen any here. That's probably a good thing, probably makes all of you feel more

comfortable. But it's one of the reasons why I feel privileged to be here.

Okay. What are some of the challenges that we face in this? I mean, this is the crux of the matter. Money drives everything. And, you know, we talk about research and we talk in a disconnected way about changing things, but without money, without some plan to get things done, nothing will happen.

I think Colleen Boyle mentioned that one of the issues that families brought up in her sample was insurance concerns. And one of the clings we face is inappropriate research and eligibility criteria for people with autism spectrum disorder.

In my home state of Maryland, it was legal for many years to deny services on the basis of those services that were habilitative in nature, as opposed to rehabilitative. So this is a wonderful way of denying a huge amount of services to the autism population, autistic population, because those services were by nature habilitative.

We were fortunate. We got some changes, not a lot of changes, but this is the sort of sometimes

subtle restriction that families face in providing services to their kids.

Another challenge is inadequate benefits in public and private insurance companies. I never met a family that didn't have a complaint about the limitations on your insurance coverage and how much they're out of pocket for providing services to their kids.

Inadequate provider reimbursement for appropriate autism spectrum-related services — this is a huge issue at CSAC. We are always struggling to maintain our financial viability because our reimbursement from the state is not really adequate for the population we serve.

The state does not seem to recognize, the State of Maryland does not seem to recognize, that persons with autism spectrum disorder present more challenges than, say, a Downs syndrome population. So we're always begging for money. And seldom do we get the money that we need.

Lack of flexibility in publicly financed services programs — the Medicaid rules, in addition to being enormously complex, present some

challenges for the community, autism community.

The Centers for Medicare and Medicaid Services view the Social Security Act as denying Medicaid waiver reimbursement for special education services that are provided by a local education agency.

The problem with that view is that it shifts the burden, financial burden, on providing services to the states, which are terribly depressed and which, unlike the federal government, do not have the resource of printing money. I wish it did.

Now, Cathy mentioned an inconsistency across states and the lack of mechanisms to pay for services. We live in the most balkanized system imaginable. Every jurisdiction is different.

Counties are different. Families in my State of Maryland know that if they move from Montgomery County, where we're here now, to Howard County, there may be a totally different picture.

This is a crazy, crazy system when you're dealing with an extraordinarily needful population. You, in essence, move to a foreign

country when you buy a new house.

Lack of assistance to families in providing for the financial needs of individuals with autism spectrum disorder — families need assistance in planning and I was thinking about this the other day. You know, the American Bar Association, the local bar associations provide some help, but I don't think that there has been much of an organized effort, cohesive effort, to educate families about what they are going to face down the road. We can do a better job on doing that.

So what are our recommendations here? Here is where the research community can help us: demonstrating the cost-effectiveness of early intervention. By doing that, we're less likely to have claims denied for experimental services.

Expand health insurance benefits for autism spectrum disorder, taking into account the need for a broad array of services. One of the problems is that there aren't a lot of products on the market, insurance products on the market, for the population of persons with autism.

I'm not sure why that is. I'm wondering if

it's in market disequilibrium that the people who provide those insurance packages don't realize that the autism community very much would buy into specialized insurance products.

Another recommendation is develop model financing, public/private insurance packages, and Medicaid waivers. Again, I think we need to sit down, public and private groups, and develop programs that are going to ensure that more people are getting services. And the financing for those programs may be public or it may be entirely private.

Families are willing to pay for services for products, but the products aren't out there. We need to conduct a national study of costs and insurance to determine policies and practices that affect financing, eligibility, and service delivery. We don't really know about all of those factors.

Then, finally, adapt innovative approaches, such as use of tax-exempt medical savings accounts and financial planning assistance and blended funding strategies.

One of the projects that Jon Shestack and I have worked on involves something analogous to the section 529 plan, so most of you may be familiar with those plans. These are the college savings plans.

I have one from a typical kid, who, of course, really doesn't need assistance. He's a good student. He will thrive regardless. Yet, I get tax advantage savings for putting aside money for my A student.

And, yet, if I wanted to put aside money for my severely disabled autistic son, it would not be at tax-advantaged rates. Something is wrong with that kind of system. And I hope that we can address this.

Okay. Cross-cutting things and recommendations — let me try to sum up everything that has been said. Address urgent need for services across the life span, coordinate services across the multiple systems serving individuals with autism spectrum disorder so that families can easily access services, increase provider capacity from primary care through specialty care, develop standards of

care for screening diagnosis, treatment, other services, expand public and private financing mechanisms to ensure that individuals and their families can access autism spectrum disorder services and work at the state and community level to foster creative approaches to expand service capacity at the national and local needs.

I think in our discussions we should not forget that states have a huge role to play in providing the services for persons with autism and that the states have historically been the laboratory for social experiments in the United States.

We tend to look at autism services as driven from the top, but I think that if we're going to expand the services that we provide to this population, we are going to have to do a better job in getting the states to devote resources and their creative energies to providing services.

Okay. I think I'm up to my last slide. And if I don't mention this, then I'll be in big trouble. This isn't just about money. It's very easy to come up here before this kind of audience and say,

"We need more money for autism services" and have everyone sort of agree. You know, that's a wonderful thing. We can all agree on that.

But it's more than just about getting additional dollars. What we need to do is we need to harmonize the providers with the people to whom services are being provided.

We need to get insurance. We need to get insurance companies around the table. We need to work together in a more unified way so that families that want to provide services for their kids can.

Right now in many instances, the services are simply not available. I cannot send my ten-year-old son to a camp during a school break. And I'm in Montgomery County, which is, of course, one of the wealthiest counties in the United States. There is no holiday camp for children with autism.

My typical kid, I could probably send him to a choice of four different basketball camps, three different baseball camps, but there's nothing available for my son with autism. And I'm perfectly willing to pay for that. We need to do

some better coordination.

Okay. Now, what are our practical next steps? Submit expert working group draft, autism, ASD road map, to IACC Services Subcommittee. I understand that this is going to be done around the end of the year, beginning of next year.

And convene the expert working group and representative agencies from the Services Subcommittee, develop coordinated implementation plan. And I think it will be important at that next step to pull on people from specialized areas, like the insurance industry; finally, present final ASD road map and implementation plan to the IACC at the May 2005 meeting.

That's it.

[Applause]

Dr. McPherson: I think we left a half an hour to give you a chance to raise questions, talk about other dimensions, whatever. And I will field them and pass them on to our experts here. Yes?

Dr. Gordon: I really congratulate the committee or subcommittee or whatever moniker you want to use, sub-sub-subcommittee, on tackling

these very difficult and very broad issues that are of critical importance to every parent of a child with autism and, for that matter, of the sibs of children with autism, too, because they are wondering what they are going to do when their sibs grow up, I'm sure.

You have also pointed out that there needs to be a driving force. I mean one reason why things are fractionated, both historical but also nobody may be taking responsibility, partly because they can avoid responsibility since no one knows what actually works best.

I wondered to Stuart and the other members of the committee, does the natural disparity in services between different communities, different states allow a tentative experiment to see what the outcomes are like when they're doing better versus worse?

In other words, in order to motivate a change, you would have to show that the change makes some difference. The change is going to be expensive. There's no question.

You've pointed out that there is a wide

disparity in services. Admittedly, it's an imperfect experiment. But would it be conceivable to examine, stratify different communities and show how a DDR did not make a difference depending on what kind of services integration was available?

Dr. McPherson: Go ahead. David is a researcher, and you're talking services research.

Dr. Mandell: There are two papers coming out at the beginning of next year. Part of the problem is what is your unit of analysis? I would argue that to do this really, really carefully, you need the units of analysis to be the school district. And to do it really, really quickly, you need the unit of analysis to be the state.

There's a paper coming out in the beginning of next year showing that how much school districts spend per pupil is directly associated with the number of kids with autism that they identify. And there's a paper coming out that uses the state as the unit of the analysis next year showing that the more pediatricians there are per capita and the more school-based mental health clinics there

are per capita, the better job we do of identifying children with autism.

These are really, really gross measures. And they don't let us know what the policy is. To a certain extent, they just explore the variation. They don't tell us what the policy change is that need to be made, but I think that they show that, even at the gross level, you can identify areas where you could then drill down and see what the specific policy mechanism is that is making a difference.

I would argue that there are other mechanisms we have for doing that as well. SAMSHA and HRSA offer demonstration grants. If you look at the systems of care model, where there are 85 systems of care settings for children's mental health in 46 states and then there is an NIMH program announcement that offers the opportunity to then study in a systematic scientific way the effects of some of those demonstration grants so that you create the incentive for trying a change and then examining its effects prospectively.

I'm a little concerned about the types of

cross-sectional analysis that might lead us to make quick policy decisions, but I think that there are mechanisms to look prospectively at how these things happen.

Dr. Gordon: I'm just a little concerned that the data you report is coming out would argue that what they ought to do is stifle all services. And then autism would go away. The less you would spend on physicians, etc. you won't see any individuals with autism.

I had in mind something, again very imperfect, that if you do something like a case control study -- I mean, there are communities — there are schools that have been doing this for a long, long time and that it might be possible to retroactively, retrospectively, see if you can match individuals and see how they came out differently or not.

Dr. Mandell: Specifically outcomes.

Dr. Gordon: Well, outcomes, yes. In others, to drive this question of whether services should be provided in the sense of what is the outcome of doing things right, as we imagine to be done

right, versus the outcome of letting it happen haphazardly, as it typically is happening. Can you demonstrate a real difference in that?

It wouldn't be perfect. Obviously it would be very imperfect because it would be retrospective. It would be case control. It wouldn't be experimental. And it would be relatively small n. But it might at least be a demonstration project to show that it's worthwhile to accomplish this, either at the level of individual adult, formerly child, getting better or the level of less cost to society as a whole from such an individual having coordinated services, even though the services cost more for that individual.

Dr. Mandell: Right. And we'll let Cathy answer that, but I do want to point your attention to the article that came out two years ago in the British medical journal on the lack of effectiveness studies on parachutes and, therefore, that perhaps that's not an appropriate intervention for us to be using for breaking people's falls.

I don't think we want to hold up services for -- I'm not sure in some ways that we have time to

effectively research some of these things prospectively before we start making some of the basic changes in systems.

Dr. Gordon: By the way, don't get me wrong. There are a lot of interventions we don't do because who wants to volunteer to be a control group --

Dr. Mandell: Right.

Dr. Gordon: -- like the parachute one.

Dr. Mandell: Right.

Dr. Gordon: I'm just trying to think of what would motivate somebody who actually has the wallet to pay for these things. One way would be to show that it makes a difference. And in a sense, you're sitting on a pool of imperfect data already collected in a sense, existing adults who grew up in different communities with more or less services. That's what I'm suggesting. I don't know if that is a feasible idea or not.

Dr. Pratt: I can tell you in Indiana, we have been interested in how do you bring things together for individuals. And, you know, this is not scientific. It's really looking at case

studies, examples of folks.

I have to tell you that I have a very personal interest in some of this because my mother is in a wheelchair. And she is in her home. And some of the things that I know are that nobody will love her as much as I do and that it does take a community to support her, so much of the community, as a matter of fact, that we have people in and out of the house all the time. And an elderly neighbor asked us recently if my mother was dealing drugs. I told that she's not. I hope that's true.

[Laughter]

Dr. Pratt: One of the things that we have done is really realizing this concept that families are often the people who this falls on, either emotional or financially. So how do we support them in their mission and vision and ideals for their sons and daughters? And so we have done a lot of work with doing person-centered planning and doing circles of support.

What that has done is that it has pulled together communities of people. And we have done

this in large urban areas. We have done this in rural areas. We have done this in areas that have lots of services. We have it in areas that don't have a lot of services available.

And the idea is that when families only have themselves to draw upon to make these things happen, they oftentimes don't see the opportunities available.

I can tell you from the situations that we've been involved with, the impact on individuals' lives is that these are children who are now successfully going to school. These were tough kids before, but they are successfully going to school.

Their family feels supported. Their family sees resources that the children are involved in community activities that the family never dreamed was possible. And the other side effect of it is that now these groups have expanded so large that they sometimes have to find large rooms to do this.

I think that I realized as a child supporting her mother that no federal agency and no financial

agency was going to be able to do what I could do with my brother and with my family. How do we help families to be able to pull together those resources?

I think the outcome of it has also been that families have utilized fewer financial resources as a result of that because they have made more community resources.

I think there are examples of that that are happening around the country. I think that not all of those examples are in the autism community. I think that there are examples of that in the community with people with severe disabilities.

The other side effect because I have been doing this for a long time is that what we see is that when we get folks kind of engaged with folks on the autism spectrum or people with disabilities, that as they become adults, job opportunities occur. So it really is kind of engaging that community, but I do think we have some cases of that.

Dr. Mandell: The short answer to your question, which we didn't answer is yes and fund

us.

Dr. Pratt: Fund us because we would like to do more.

Dr. Mandell: The short answer is absolutely yes. I'd be a little concerned about sampling purely on outcome. And I'm not sure exactly how we would define that, but in terms of, say, symptom reduction. I think absolutely there's been no study like that.

Dr. McPherson: Tommy, did you want to comment?

Dr. Insel: Yes, some comments and questions. First of all, I thought this was a spectacular effort. And, Merle, your report is very, very helpful and makes us think about a lot of things that we haven't talked about here. I'm not sure how many of them we'll get to deal with today.

Having been on the President's New Freedom Commission, a lot of this is very familiar. It's not in any way unique to autism, but these are generic problems that we deal with for services across the spectrum. And, as you pointed out, part of that is that the center of gravity for services is at the state and local and family level. And we

often look from the federal level trying to figure out how can we have any impact here? As you note, there are things that can be done and can be done much better.

One of the places where I think there might be some traction in this immediately would be to point out what it is costing us to do things the way we do them now. And I am really impressed by this graph, which I had seen once before. It's the third slide that shows the increase in special ed, the number of kids who have been getting services through schools.

If you were to just begin to project that out to age 18 and then to begin to think about this idea of falling off the cliff, what will the cost be for social services and for 18-year-olds going forward?

I think you could make a very strong case about not just the public health challenge here but the phenomenal economic challenge that is looming out there unless we do something about it in the short run. So that kind of data, there may be already models to yield a lot of what you need

in hand.

The question I have for you is, as I look through the recommendations, a lot of what is there -- not a lot but part of what you have under almost every one of these is the developing guidelines, guidelines for diagnosis, guidelines for standards of care, guidelines for access, all of those issues, which are great. Who do you think should do that? Where should the guidelines come from knowing that we've got a lot of the people around this table who probably could have a role here?

Mr. Spielman: People are looking at me, and I'm probably the least qualified person in this. I'm closest to the microphone. So I guess I will have to address the question.

I think the federal government can give incentive, not necessarily of the financial sort. During our lunch break, we were discussing the presentation and the role that this body could have in bringing some people to the table to work on some of the issues that we face and try to come up with some of the solutions to the problems.

I'll go back to the lack of appropriate insurance products. I do not believe that there has been a meeting with the community, a high-level meeting with the community, and the insurance industry to talk about the market for the kinds of products that we in the community really need.

What strikes me is that there is always going to be an insurance product for a specialized market. I have dental insurance. It covers next to nothing, but there is a product out there. I have long-term care insurance. There is a product out there.

I think that this body, in addition to -- I know this body can't write checks, which is really unfortunate, but I think that this body can by its nature as a multi-agency body help us in the working group to bring together people to develop guidelines on a whole range of subjects.

Dr. Insel: Okay.

Dr. McPherson: Lee and then there is --

Mr. Grossman: Tom, to answer your question, ASA could do this. We could put together the

experts. We could put together a plan to make this happen. There are other people who could do this.

We're running out of time. We have run out of time. We produced four years ago the economic impact of autism and its cause on society. NIH has been saying for the last six years that this is a medical and national emergency. The Department of Education has said that this could possibly bankrupt the public education system. Time is done.

ASA as well as others could bring together the groups that are necessary to put together a plan that is needed today to get moving on this.

The comments I receive when I go up to the Hill, they want a plan. They want it today. They are ready to act on it. They know what this means to the country.

ASA, as I said, could do this. I was involved in our expert workgroup. We discussed what best practices were. There was pretty much an understanding -- and correct me if I am wrong -- that we know now what in 2004 best practices are and what they mean.

We also understand that that will evolve as outcomes are measured and as services and interventions improve and expand and increase. But the point was to get moving now and to move forward.

Dr. Insel: What has kept this from happening?

Mr. Grossman: I think that there was a willingness to move ahead to address this as it should be done. What was most impressive to me at the workgroup was that we had experts who were brought in.

We had advocacy agencies that were sitting there. We had people on the spectrum sitting at the table. And most importantly, we had Merle and Sybil and Gail and others at the table that were committed to this process.

That was a significant step forward that all of these groups were together committed to moving this forward. And I think now that we are beyond that and that we do have this commitment, the only thing that is standing in our way is just someone to be given the green light to start producing what needs to be done.

Dr. McPherson: Is there a question over here?

Dr. Geller: I'd like to commend the committee on the report, and I'd like to make one little suggestion for perhaps tweaking it a bit. And that is just looking at it now to try to tweak it a bit so that we are including the whole broad spectrum of autism.

It's particularly important that those people with IQs over 70 are so frequently denied services just for that, just for that one aspect of their functioning, in many states all over the country.

And, as we all know, the difference between an independent and a dependent adult is millions and millions of dollars of federal, state, and local money, never mind the quality of life issues, which are, of course, more important, really, on an individual basis.

But, financially speaking, the difference between dependence and independence makes a huge financial difference. I think at least that sort of thing could be -- well, as you say, we know how much this costs. It's not a mystery.

But when you talk about -- you know, you don't

know when you have a child if they're going to end up being a dependent or an independent adult. We really can't guess yet. But as people become adolescents and young adults, we begin to kind of know.

How can we push more people into independence from dependence? I mean, there are people with Master's degrees and Ph.D.'s with Asperger syndrome who are dependent adults. I mean, that's crazy. What can we do to push more and more people at every level of functioning from dependence to independence and what does that save us and how can we do that?

So I think that as you are putting your report in its final stages, I think it is important to look at not just the IQ functioning but a lot of the different kinds of functioning of the whole spectrum of people.

We know there are people who are always going to need a lot of dependent care forever. Those people exist. And then there are middle people and higher-functioning people cognitively. And they have very different needs.

So I just think I would like to suggest that we make sure that all the levels of people are being addressed by your report.

Dr. McPherson: I want to reinforce that what you heard today was a status report on a road map that is being built. And one other thing is that we did get from the expert workgroups all the best practices. We just didn't put them in here today, but they will be in that final road map that you get. So we really did talk about what we had.

Jim?

Dr. Hanson: I, too, have found this to be a wonderful kind of session and something I think was badly needed. I have a couple of questions and comments. One is to you, Merle.

I don't know where things stand with the new addition of Bright Futures, but it was my understanding that perhaps there was going to be some focus on children who had things that would exclude them from the general category of normal. And I wondered if there was any thought about trying to include some of this for autism in that document, which would be widely distributed and i

think used.

Dr. McPherson: Funny you should mention that. It is being revised by the Academy of Pediatrics in a fairly complex way for each age group. Bright Futures are national guidelines for prevention and well child care and early identification, that kind of stuff.

We have been working very hard with them on all of the sections to for the first time have national guidelines that are inclusive of children with disabilities in the world and --

Dr. Hanson: And this would be a wonderful opportunity, it seems to me.

Dr. McPherson: Yes. Actually, our whole work this weekend for me and my staff is going through all of those and providing by next Tuesday the final comments on the revised Bright Futures to see if we can incorporate. So we will take a look at that.

Dr. Hanson: Yes. The other thing is, whereas, I understand Lee's patient on this, I'm not sure, actually, that we have as much data as people once they start looking at the cost will insist upon

having. I mean, if as a political action you can get it done, that's wonderful, but I think in the long run, we ought to have better data systems.

And Denise Dougherty might want to comment on what is best related to autism you can find in HCUP or NHANES or any kind of national hospital inpatient/outpatient or other discharge system because I think I know the answer.

And why not start to put some of those items in, like in HEDUS report cards for Medicaid managed care systems or work in a voluntary way with Kaiser Permanente or other groups to establish these data sets?

One of the reasons I say this is because somebody said the phrase "cost-effectiveness studies." I would be very, very leery of hanging my hat on that because depending on what you add in and how long you add it in for, you can find out that, in fact, it is not cost-effective. And I think that that would be unfortunate to have that outcome.

Part of this is that we should do it because it's right, even if it is cost-effective. The most

cost-effective system is to let children with birth defects die. And that's not exactly what I'm weighted to. I hope nobody else here is.

Dr. Dougherty: You're right about the data not existing. One thing I would say, though, I think guidelines are a necessary first step. And there are people who know a lot about the financing, especially Medicaid and how it's all done, who could work with the group and then come up with some specific action steps that could be taken to improve things, you know, what's covered, what not covered, that kind of thing.

And the other thing is you need implementation strategies to get anybody to actually use guidelines.

Dr. Hanson: This is one of the areas where making common cause with an awful lot of other groups might really work. Nationally screening initiatives have been facing this. The muscular dystrophy research programs are facing this. CDC has people that are trying to evaluate this as well. And I think all of these groups should work together towards some of those common ends.

Mr. Grossman: Part of the dialogue in the expert workgroup was in developing this national road map or this plan, there would be a mechanism to capture data so that we could evaluate the outcomes and look at it. And I think David or Stuart was going to address that.

Mr. Spielman: I just had a reaction to comments you made about that cost-effectiveness only is part of what we have here. It's difficult to talk about morality and ethics because those are so difficult concepts for people.

But I have been told that early hearing screening is not cost-effective. Should we not do it, therefore? Should we measure all of our health programs by the standard of whether there is some economic benefit to be gained? That would be a very cruel yardstick to use.

I mean, I hope we haven't reached that sort of Hobbesian point where we're measuring everyone by their economic contributions to society.

Dr. Hanson: I certainly concur with that. Obviously if you look, I think CMS can probably comment on this where an enormous fragment of

health care dollars is expended in the last couple of months of life. So that's an analogous point, I think, but I do think we need to start collecting the data so we actually know.

I would like to mention that there is a meeting being planned in mid-January here in D.C. by the muscular dystrophy research centers that is going to address the issues of burden of disease. It might be worthwhile for someone from this group to sit in on that and listen to those burden elements in terms of planning your own activities. I think we can get that done.

Dr. Mandell: In 2000, Medicaid paid for services for 37,000 children with autism. The HCUP database has information on thousands of children who have had hospital discharges who have been diagnosed with a primary or secondary diagnosis of autism.

And since the number of states in the HCUP database that have allowed us to link kids, you know, create an identifier so we can follow them across years has increased, we have a lot of opportunities with existing data sources, I think,

to look at some of the costs associated with children with autism.

Dr. Hanson: Yes, but it is inpatient data, no outpatient data.

Dr. Mandell: But the Medicaid data isn't and --

Dr. Hanson: No. I understand. I'm just suggesting that there really isn't an adequate --

Dr. Mandell: Right.

Dr. Hanson: -- set of items on most of these disorders.

Dr. McPherson: Tom, I need to ask a question because it's 3:00 o'clock, and I know we don't want to steal anybody else's time. There are a number of hands around the room that --

Dr. Insel: Let's take two more minutes, maybe quick questions.

Dr. McPherson: Someone down there has had her hand up and a gentleman here.

Ms. Dunkle: Yes. My name is Margaret Dunkle with George Washington University. And I'm working in Los Angeles County.

I wanted to get back to the issue of the

federal role and what this group might do. And I just had a couple of thoughts about taking advantage of some current opportunities.

The Higher Education Act is coming up for reauthorization on the Hill. One of the things that we do know is that medical schools, other schools are not in most cases teaching, for example, the most effective screening tools, developmental screening tools.

To the extent developmental screening is taught, they generally use the Denver, which is a poor quality tool, rather than key pages and stages of the Child Development Inventories, which had been recommended by the American Academy of Pediatrics and Child American Association of Neurology.

So one of the possibilities is through the Higher Education Act and the administration's position on that, which we will be resubmitting, I presume, is to make recommendations about accreditation, certification, licensing types of issues under the Higher Ed. Act.

The second has to do with programs such as the

HeadStart bill, which is also being reauthorized. Right now HeadStart requires within 45 days of a child's enrollment into the HeadStart program that they have developmental screening but doesn't require that it be of high quality. It requires it to be culturally competent but it can be equally poor quality for kids of all cultures, I guess.

One of the things that we have done in California is we have come up with a psychometric definition of what constitutes a high-quality developmental screening tool. Jose's shop, CDC, has commented and given us some very helpful comments.

Basically we have a solid definition, so just a simple insertion. And this could be an administrative position, administration position of inserting high-quality developmental screening, as opposed to just screening. And then clarifying what high quality was in terms of its psychometric qualities by a colloquy or report language could make a huge difference and also have great implications for EPSDT and others. So those are just a couple of specific ways in which this group

might influence in a positive way the federal role.

Thank you.

Dr. McPherson: Thank you.

Dr. Insel: Actually, given the time, Merle, we probably need to break at this point. Since other people may have similar sorts of recommendations, what would be the best way for them to convey those recommendations to the working group? We may need to --

Dr. McPherson: Bring them back to the chairs of the Steering Committee. We are working with both the expert workgroup and the subcommittee. We will be happy to take those, either from Sybil's or mine. That's probably the best, right?

Dr. Insel: Ann, do you want to?

Dr. McPherson: Or Ann.

Dr. Wagner: I think that people could send comments by e-mail, probably to the IACC. And the IACC Web site has an e-mail address.

Dr. McPherson: That would be wonderful if you could do it there. Might I mention that we are also supporting through contract the work that is

being done with the expert workgroup. And we have Beth Roy here as our contractor. And those could certainly go to Beth, too. She is doing a terrific job for us.

I will finish. I just want to thank the panel enormously for a wonderful presentation. I want to thank them for all their work they have done to bring us to this step and to the expert workgroup as a whole.

It's been a wonderful group and also to appreciate the willingness of all of the federal agencies to hang together and try to figure out who to move this forward.

So thank you very, very much.

[Applause]

Dr. Insel: With that, we will break until 3:15. So ten minutes, and let's get back. And we'll start on the screening.

[Whereupon, the foregoing matter went off the record at 3:04 p.m. and went back on the record at 3:17 p.m.]

Dr. Insel: If you will take your seats, we are going to start on the final presentation. You have

a difficult act to follow. Dr. Deborah Hirtz will give us the update on the Screening Subcommittee.

Dr. Hirtz: That certainly is right. It is a hard act to follow, but, actually, in a way, it is made easier because there is so much overlap between the two groups. And I think all I am planning to do today is just give you a brief update on the meeting that we had yesterday and the progress of the Screening Subcommittee and its interactions with the Services Subcommittee and kind of where we stand and what our plans are.

We did have a very useful meeting yesterday that included some consultants with experience with successful early screening programs. What we focused on was trying to develop a road map but, again, a road map that's very much focused on implementation and how are we going to move forward and get some of these things done. Some of them already are being done. You heard about the autism awareness campaign. And I think that there is a great deal of activity around early identification of developmental disorders and autism already in the works.

We did work on a road map. We did decide that it would be crucial to integrate this with the implementation plan from the Services Subcommittee. And we plan to finish that draft together.

So the basic intent is to promote early identification of the autism spectrum disorders as well as other developmental disabilities with a focus on screening and identification, early identification, of autism. The goal is that all children should be identified as well as be an appropriate intervention by the time they are no older than age three. And we did talk about wanting it to be even younger.

The other thing that we wanted to make sure that we stress is that screening is not just something that happens at age two in the pediatric office, but this should be an ongoing process of being aware of developmental issues as part of health issues throughout childhood and, in fact, even beyond.

So the critical components of an early identification initiative are to promote and

improve the practice of early identification on a broad systems level kind of approach.

So the matrix has four different areas. And I'll talk to you a little bit, in a little more detail about those, the awareness, the practice of awareness. And that involves the practitioners and families, practice of screening, what kinds of methodology to carry that out, what kind of resources and policies are needed to make the services available, and how do we monitor how effective what we're doing is.

So this is kind of how the grid looks as a picture. Again, we want to emphasize the link to intervention. In fact, that is not just a wish. That is actually, as we have learned from our consultants who have been involved in successful programs, the only way that their programs have been successful, that there is no way to separate out having a successful program for screening early and being able to offer at the same time the next step and the services that go with the identification.

So the framework was really to look at what is

being done, what else can be done. We wanted to think somewhat along the lines of the model of the research, autism research, road map about time frames and priority. It doesn't necessarily have to follow exactly the same pattern.

In addition, we wanted to make sure that we thought about and proposed for implementation purposes agencies, groups, organizations that would take the lead and take responsibility for having certain actions in certain amounts of time. So there would be a real implementation plan.

So first in the issue of awareness, there is no question that there is a lot of work to be done involving families as well as involving providers at different levels. Some of that, as I say, is being done in the autism awareness campaign authority underway. And I think it's underway very effectively, but we also need to focus on reaching the providers. Part of that involves education, and part of that involves sort of being able to offer a complete package of what providers can do once they do the screening and identify a problem.

Most importantly, clearly the parents -- and

this is also documented by research. And this is what our consultant said yesterday, that parents' concerns will the vast majority of times be accurate. And we have to make sure that people who are caring for children, medical care, listen to the concerns of families.

Screening practices involve what kind of methodologies we use to screen, what kind of screening tools, how it's done. Do we use parent questionnaires? What is the best and most effective method? We need more research, but we also have effective tools today. And we don't need to wait in order to implement this screening. We just need to improve it as we go.

The useful strategy was felt to be investigate very thoroughly whether they're at the state level or community level, county level, those that have successful models of early screening through provision of services and not to necessarily apply those universally or throughout the country but to look closely at what are the elements of those communities that could be analogous or translated to other communities that don't have this program.

And it certainly won't be one size fits all, but there may be several different models that would be depending upon the population and the situation in other counties or states that could be applied from those that are now successful.

For resources and policy, we talked about the political and economic arguments in favor of screening and referral, much the same as we have been talking about in services, that really the cost-benefit of doing this effectively is great and needs to be emphasized in order to make a real policy change. And the political and economic obstacles need to be addressed.

Then the fourth component was that we need to have in place a way to monitor the outcomes of what screening and services we put into place. Again, that provides the information on cost-benefit and information on success. We need to continuously evaluate what we're doing and show that it is beneficial in not just economic but all ways.

Now, as overlapped with the supporting features that have been discussed with the

Services Subcommittee as well, these four ideas or features need to be kept as part of the framework of what has to happen and what has to be available in order to make this happen successfully, the medical home concept of care and organized care and coordinated care for each child. If the services are not available, the screening programs will not be successful, nor will they be, in fact, useful. We have to make sure that that is part of the whole package as well as a system of support for families.

An example was given of how in the State of Connecticut physicians can refer if there's any question on screening. It can be parental concern screening or physician or provider concern. There is a 1-800 number to call, but that gives not only a referral, but it provides support for families at each step of the way and what they do next and where to go and is a comprehensive family support system. And I don't have to say much about the need for services to continue through the life span. We certainly have touched on that, and it's crucial.

Now, you actually saw this slide before in the services talk, but I just wanted to put it up again because we discussed it yesterday just to emphasize how much overlap there is and how intertwined the issue is of early screening with provisions of services and that all of these issues, family and professional partnership, they're all both services and screening issues.

I think that's it. And I would be happy to take any questions, but, actually, first what I'd like to ask if Dr. Cordero or anybody, Dr. Rice, Dr. Crew, anyone who was at the meeting yesterday, would like to make any further comments.

Dr. Cordero: Thank you. I just wanted to sort of highlight a couple of things that Deborah mentioned. I think that some of the key points here are that even if we talk about screening or we talk about early identification, we really are speaking about a system.

And children need to be recognized early with autism, but they need to be integrated into the appropriate services. That goes for evaluation, diagnosis, and treatment.

It is really that continuum that actually needs to be in place. So it is really critical to have not only sort of an appropriate process for recognizing the children but also to ensure that services are in place That's something that Paul Dwoskin in Connecticut actually described very well. And it was great to see actually two models, one in Connecticut and another in North Carolina, that actually are being able to do that.

That links very much to the Services Subcommittee. That needs to be emulated basically in every state, and that is a challenge. That is an urgent issue that we need to address as soon as possible because we need to have something that begins to be in place as we develop an awareness campaign.

I think also I would like to point out that there is linkage of what we are doing in terms of early identification with also the research part. One of I think the key benefits of having children identified early is that is going to give us a cohort that actually could be available for answering many of the questions from what works

for treatment but also large numbers for addressing many of the questions that were raised here earlier today.

Dr. Insel: If you could identify children earlier and you had, let's say, three times the number of three years old coming into treatment, are the services available to them?

Dr. Cordero: I think the answer is no, but, on the other hand, I think one of the points that Paul Dwoskin made very clearly yesterday is that the kinds of issues that you tend to observe at an earlier age are not as sort of functional deficits that may not be as serious as if you would get them at five that although you may not have as much services for the kind of functional deficits, it can probably be done and that their experience in Connecticut has been that, even with more children with the severity and the issues that need to be addressed actually are more manageable than when you have older children.

Dr. Houle: I would just like to speak to your question, Tom, that oftentimes, at least in the early intervention system that's administered by

education, the appropriation is based on the number of children who are identified. So it's kind of a chicken and egg thing.

You wouldn't want to not identify children because there was a lack of funding or services were under-funded or children were under-served. If they need services, you want to continue to identify that need, which is possibly one of the ways that the appropriation would be raised, then. That would be justification for preventing additional funds for services. So it's a chicken and egg kind of thing.

Dr. Insel: Great. That's important. Just to clarify from this morning -- and I guess your subcommittee must have worked this over extensively -- do we have the instrument we now need with the sensitivity and specificity to do this or is that still something we need to develop before we can move forward?

Dr. Hirtz: We do have adequate screening instruments. We have a range of them. They can always use improvement. I think one of the issues is not just the instrument but how best to

administer it. It's clearly easier for a busy pediatric office to have a questionnaire that a parent can fill out while waiting in 10 or 15 minutes than it is to have a more detailed, longer questionnaire or screening tool that would be administered by a professional.

So there is a range of instruments, and there is plenty to work with now. We need to improve the options, but we don't need to wait.

Dr. Cordero: I just want to add that I think that we had an extensive discussion, actually a couple of hours of this. One of the points that emerged is that the real barrier in terms of screening is not really the instrument but just the lack of time for having something that really could be integrated into the current health care and something that is quick and probably is better than something that would take half an hour, which would be unlikely that provokers would use.

Dr. Insel: Other questions or comments?

[No response]

Dr. Insel: Thank you very much. Now we're in the final phase of this particular meeting, which

is phase of public comment. And we would ask that those of you who have public comments come to the microphone or you can come to the table. It's best if you can begin by identifying yourself. Thank you.

OPEN SESSION FOR PUBLIC COMMENT

Dr. Ahearn: Hi. My name is Bill Ahearn. I am the Director of Research at the New England Center for Children.

The New England Center for Children is a service provider that provides educational and clinical services to children from about 2, a little younger if we could get them, up to 22. And we also have a very small adult component that we sustain, even though its financial viability is oftentimes a little difficult.

We at the New England Center have attended a number of these meetings, starting with the autism summit in 2003. We have found these meetings very informative, and we have been very impressed with NIH's structuring the research matrix and the carrying out of the road map that has followed.

Now, the START and the Collaborative Programs

of Excellence in Autism are certainly great strengths and have been very productive. One of the things that strikes me is that weaknesses that we have are also brought up here.

I think one of them you just brought up, Dr. Insel, the outcome measures that we get from screening tools. Screening tools are not sensitive enough to tell us if we're making gains, but I'll touch on that in just a moment.

These topics are openly discussed here and seem to foster the work of others. One of the things that I'd like to remark on is that we made a comment at last May's meeting focusing on children and families currently affected by autism. Unfortunately, many of these people are not going to benefit from the research endeavors of the IACC, as the comments of a few people here have suggested.

And one of the things that we suggested at that time was accelerating the service provision matrix and road map so we can avoid adults and children with autism spectrum disorders being left behind because they certainly are.

If we had children with cancer that were being untreated or being given inadequate services, we certainly would have thousands of people on the lawn of the White House demonstrating because their children are not receiving services. I think that this is just as important of an issue that deserves the funding and resources necessary to provide effective interventions.

Now, we certainly realize that the complexity of this endeavor is probably much greater than the one undertaken to develop the research matrix and road map, but its impact and relevance are probably going to be even greater.

In last May's meeting, Dr. McPherson commented on how improvements in screening and early identification may overreach the treatment capacity of, say, the collaborative programs of excellence in autism. This is certainly an astute observation. And I don't in any way want to appear to denigrate what I feel is certainly a very insightful, thoughtful, and passionate approach to developing a services matrix and road map, but this vastly understates the problem.

There are many skilled clinicians who now allocate their resources to research, but there is a general shortage of clinicians with supervised experience in providing directed instruction to individuals with autism.

What we need to do is we need to recruit, train, mentor, supervise, and certify experts in providing educational services to individuals with autism.

Now, in 1999, the New York Department of Health published a report produced by a panel of experts that was looking to develop assessment and intervention guidelines for young children with autism. This panel concurred with Dawson's and Osterling's 1997 identification of six comment elements of effective intervention programs.

I wasn't going to mention these, but since we had a bit of a discussion on intervention programs, I want to mention them now. These are: number one, a curriculum that addresses social, verbal, and other key deficit areas in autism; two, a highly structured teaching environment that is generalizable to the natural environment;

three, the use of predictable routines, which perhaps would be very useful for typically developing children as well. Four is a functional approach to problem behavior. Five is preparing the children for public school services. And the sixth is fostering family involvement in intervention.

Now, to hit on another theme of today's meeting, I am going to tell you what I am, take off my sheep's clothing. I could be like Bertram Russell and tell you why I am not a psychoanalyst because I am a behavior analyst. That is because I like outcomes now. I like behavior now to change. to change at the point in time in which we are intervening.

Now, the reason that applied behavior analysis can be translated into successful behavioral and educational programming, which addresses all of these areas, is that applied behavioral analysis is an individualized approach to providing directed instruction.

Applied behavioral analysis is not magic. There is no one curriculum that is representative

of applied behavioral analysis. It is applying what has been learned and the basic science of learning theory to providing instruction to those individuals that have skill deficits and problem behavior.

Now, ABA is an individualized approach that involves careful assessment of each child and the skills, their skill deficits and problem behaviors that interfere with learning and typical social functioning.

Now, in fact, it's that careful assessment of a child's current behavior and individuals' current behavior that is most important for developing a successful curriculum for that one individual child.

Besides the obvious need for brief user-friendly tools, like the M-CHAT, we need more comprehensive assessments to drive individualized curriculum and to be sensitive to the gains that children are making. The ADOS, IQ tests, and so forth, are not sensitive enough to show that children are making progress.

Now, someone mentioned individualized

education plans. And they are very important. The objectives in them, however, are only as useful as they are specific to skills that the child needs to acquire and to the systems for reporting objectively on whether or not the child is acquiring those skills.

Now, one potentially important research agenda is the development of a truly comprehensive assessment of all skills, social skills, play skills, verbal skills, and otherwise, skills that go beyond the core deficits of autism, because the child that is not integrated into a social unit, that lacks verbal kills, they're going to be falling behind across the board. It's not just those skills.

What it takes to be a typically developing two-year-old or a three-year-old, we need to know all of those things. And we don't have comprehensive enough assessment tools. It's those kinds of tools that will allow us to know what the child needs to be taught. And certainly at the --

Dr. Insel: We are going to need to make sure other people have a chance to talk as well.

Dr. Ahearn: I'm wrapping up right now. Thanks.

Dr. Insel: Okay.

Dr. Ahearn: We as educational service providers -- and I think the McMaster group certainly was talking about these kinds of tools -- really need to be out there. And we need to collaborate together for providing effective educational services to individuals.

Now, the last thing that I wanted to very briefly comment on is that in terms of service provision, there are ways for assuring that individuals are qualified for providing effective services. And, as I had mentioned, I don't feel that ABA is the only effective way to provide directed instruction.

However, as a field, applied behavior analysis offers certification to practitioners that requires substantial course work, supervised experience, and standardized testing.

Nationwide recognition of certification in applied behavioral analysis would certainly help parents and educational systems interested in establishing services for children with autism to

identify some of the qualified professionals who meet some minimum standards of competence.

Thank you.

Dr. Insel: Thank you.

Ms. Dunkle: Hi. My name is Margaret Dunkle. I am with George Washington University, the Center for Health Services Research and Policy. And I currently live and work primarily in Los Angeles County.

For those of you who didn't realize, which I didn't before I moved there just a few years ago, Los Angeles County has more people than 42 states. It's almost as big as Michigan, has 81 school districts, and it's kind of a world in its own.

One of the things we are doing in Los Angeles County is having a comprehensive cross-sector initiative for early identification and intervention. We have a number of efforts. We actually just put together some materials about what we're doing. If anyone wants a set, just give me your card. And I will be glad to send you by e-mail the packet of information.

The reason I got up right now is because I

want to ask a question. It's a question because of all of the thoughtful comments that I heard today and all of the kind of connections with what we are doing at the local level, although sometimes it's weird to call Los Angeles local -- it is one county -- a local level.

We are doing a lot of things here with the Health Department, with mental health, with private providers, with nonprofit groups, with advocacy groups. We have them all sitting around the same table and working together.

One of the things I would be interested in exploring -- and I'd like to know if the Committee would be interested in this -- is the possibility of holding next November's meeting in Los Angeles with the idea of the day before having a site visit to look at some of these issues. I'm sorry Dwayne isn't still here because he has been involved with some of this.

In my previous life when I was in Washington full-time, I ran seminars on Capitol Hill for bipartisan congressional staff and senior people of the administration, of whichever flavor it

might have been, around issues affecting children and families.

I would like to kind of like to take that set of admittedly quirky interests and skills to the issue of special needs, early identification, and intervention, and see if this group might be interested in exploring the feasibility of holding next November's meeting in Los Angeles and what that might take.

Dr. Insel: For years we have been hoping that Lee Grossman would make an offer like that for Hawaii.

[Laughter]

Mr. Grossman: You'd better hurry. You've got a couple of months left, and I'm out of there.

Ms. Dunkle: So I don't know if you want to have discussion now, later, or whatever, but I wanted to raise it for consideration. Again, if people want information about what we are doing in Los Angeles, I'll be glad to give it to you.

It seems to me that part of what keeps momentum going is something that kind of gives you a jump or gets you out of the ordinary or gives

you a different perspective.

One of the things that I think might just be mutually helpful is to have the kind of discussion and energy of a site visit, then going into the regular meeting the next day in Los Angeles.

So I'd like to extend that possibility. And I welcome your suggestions and feedback.

Dr. Insel: Thank you. I think we will let Ann Wagner deal with that recommendation. And she can solicit ideas or she can solicit votes online and see whether there's interest from the Committee. Thank you, Margaret.

Mr. Garvey: My name is Tom Garvey. I'm from New Jersey. I'm a middle manager and have a three-year-old son with autism.

I've listened to everything today. I thought maybe you'd want the feedback from an average Joe. So here's my disclaimer. These are just my opinions. They may contain incomplete data, little or no use or control room, and may be completely incoherent and unorganized.

I heard today that parents have discussed with the CDC concerns of trust and vaccinations. And I

cannot resist commenting on how clarification has to be made that it is not the vaccination's fault. It is one of the subcomponents of the vaccination that may be to blame.

I'm glad we cleared that up because I wouldn't want mass hysteria to break out of the pediatrician's office around the country. When we look at the ingredients of most containers of food, there is usually a long list of chemicals I do not recognize. I have trust in the manufacturer and the regulatory agencies that these are safe to ingest.

Some foods contain trans fats that cause major health problems, but we have a choice. We don't have to eat them. The vaccination program has good intentions and plays an important function in our society. While we are afraid that the public will grant the vaccination program, why not educate the public?

If the data is still relevant, why not release the information from the Simpsonwood meetings? Agencies should not hide behind the President and the legal system. You wonder why we don't trust

you. Give it to us straight.

I remember signing a form at my pediatrician's office. This form had been copied and faxed and copied and faxed and was barely legible. And I had about five minutes to read it.

I'm sure my pediatrician would really have appreciated me sitting there for 15 minutes and discussing it with him, but I don't know. I just signed it. I trust the CDC and the FDA and my pediatrician with my son's health.

Little did I know I was playing Russian roulette with my son's mind. I made a mistake. I let it go without asking one question. But I'm paying for that every day at the end of a long day when I am greeted by my wife, my pets, but not my son because my return has no significance to him.

I believe we should handle this vaccination issue like a business would. Let's make a deal. Information for amnesty, plus budget.

This Committee reports to the government. Let's amend that report and let the first line say that we have concluded that autism is an epidemic and we must address this problem immediately.

Help the public believe in you again, CDC. And do not make light of the fact that you have no solution because you are waiting for mom and dad to send you more money. That's not an insult, but in management, when I have a problem, I go to my boss. Because I am a salaried person, I am expected to come with some sort of suggestion for a solution.

Certainly Dr. Insel is not anyone's boss here, but I think we should come here with a little more enthusiasm as to how we get the money and how we cure autism.

Thank you.

Dr. Insel: Thank you.

Other comments?

[No response]

Dr. Insel: If not, then I thank all of you for your participation and your comments and your hard work. There's one more.

Ms. Hane: It's been good being here today. My name is Ruth Elaine Hane. I am a person with autism. I was diagnosed about ten years ago with high-functioning autism, although now I think you

might say I am atypical.

What I find interesting is that there are a number of us who are quite verbal, have good memories of our developmental stages, and have input in terms of a lot of the topics brought up today. But I don't see much representation on this Committee, although you have Steven Shore present.

One of the challenges that many of us have is that we appear somewhat normal. You wouldn't pick me out probably significantly in the subway station. But when I'm talking in front of you today, my face becomes paralyzed so you can't tell my feelings because my nerve here does not respond to my emotions.

I'm on the board of the Autism Society of America. Because I want to speak up for those who haven't acclimated enough to become accepted in the normal typical world, who become extremely irate if they have a Ph.D. and, yet, they cannot balance their checkbook and they can't figure out the way to get there or to hail a cab.

These folks have a lot to say. And many of them are suffering today because they don't even

qualify for normal services because they have Master's degrees and Ph.D.'s and are qualified in the commercial world as technical people.

It's really sad to think that this Committee wants to continue collecting data and delaying services. Some folks would be able to be independent, like someone mentioned earlier, if they had four hours of services. Someone would come in and ask if they had done the grocery shopping or help them with it, help them with their laundry, help them find those basic services that they need just to survive. Then they could be independent.

The other area that is very, very concerning is that many of these folks don't recognize danger and trust anyone who comes. So they're exploited. We could have services to help train people to recognize danger and who to trust.

I feel there's a lot that could be done if you would seek input from those of us who can verbalize what the needs are. So I leave that with you today to discuss.

And I support the early intervention for the

children. I have a grandson who is now eight months old. I never thought I would be at the threshold of assisting my daughter and son-in-law in deciding whether or not to give shots that have poison, mercury poison, in them to prevent a disease. So my daughter is being very vigilant and careful with her pediatrician.

It's profoundly impacting individuals, the indecisiveness of committees and doctors. So I implore you to reach deeper and collaborate with one another and share your ideas to help us integrate and cooperate.

Thank you.

[Applause]

Dr. Insel: Thank you so much for those comments. I think you point out something that hasn't been mentioned enough here. There is a conspicuous absence of people with the disorder on the Committee, though we have parents of children with the disorder.

Unfortunately, there is no one here on the Committee who has the authority to appoint members to the Committee. We have this problem that the

membership is subject to the assignment and approval of the Secretary of Health and Human Services.

Your comments remind me that we will need to go back once again, as we have now done several times, to have a discussion with that office about the Committee membership. It's a very important point.

Okay. At that, I thank all of you again. And the meeting is now adjourned.

[Whereupon, at 3:57 p.m., the foregoing matter was adjourned.]