U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE

FULL COMMITTEE MEETING

FRIDAY, NOVEMBER 17, 2006

The Interagency Autism Coordinating Committee (IACC) convened in Bethesda, Maryland, at the National Institutes of Health (NIH), 31 Center Drive, Building 31, Room 6C10, Thomas Insel, M.D., *Chair*, presiding.

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PROCEEDINGS:

Dr. Thomas Insel: I know there will be some people still drifting in, but we've got a full agenda, and I don't want to fall too far behind at the outset. I'm Tom Insel, the Chair of the Interagency Autism Coordinating Committee, and pleased to welcome all the members of the Committee and many of those around the room who will be in attendance today.

This is an interesting meeting. We'll have a variety of presentations this morning, both on science and services. You'll be hearing really the full spectrum from a presentation on service guidelines on the one extreme to presentation on a stereological analysis of amygdala in autism on the other. So I think we have a lot to look forward to.

Another very important item on our agenda today will be to go through the evaluation of the matrix, which took place over the last couple of months, and we'll put aside some time this afternoon to have a discussion with the Committee to hear more about this and to make sure we get

your input before we move to the next step. So that's the agenda for the day.

I think without taking any more time, we'll come back and do a round of introductions in just a few minutes, but let me introduce Chris Plauche Johnson, who is with us from The University of Texas Health Science Center at San Antonio. Dr. Johnson is the Medical Director of the Village of Hope Center for Children with Disabilities. It's a clinic that provides interdisciplinary evaluations of children with developmental delays, autism and learning deficits.

She's served on the American Academy of Pediatrics' National Committee on Children with Disabilities since 1997, and she's worked with AAP leadership to publish a brochure regarding the early signs of autism. She was asked to represent the AAP on the Services Subcommittee of the IACC, and that's actually the capacity in which she comes to us today.

She's somebody who has worked very well with the Subcommittee, and as you know from the last couple of meetings, we've been trying to get many

of the items on the Subcommittee's agenda to be center stage here for the full Committee.

And we've asked Chris to do this presentation. Originally, it was going to be later in the day, but because of a scheduling conflict, had to move her to the very beginning of the day. So, Chris, we're going to have you lead off the meeting before we do all the round robin of the table, and you'll sort of set the stage for us, hopefully. Welcome.

Dr. Chris Johnson: Thank you so much for allowing me to be here. I am simply representing our workgroup. It's been a work in progress for about a year and a half. There are about a dozen in our merry band, mostly representing developmental pediatricians, some general pediatricians, psychologists, school systems, parents, and parent advocates. We've had a couple of wonderful facilitators. I know Beth is here today, and also Christine who is unable to be here.

Our intent or the task that was provided to us was to do three things: Number one, to develop

guidelines for the medical home/primary-care practice in pediatrics; to develop some actions, determine or identify, I guess, actions needed from other institutes to help the primary-care/medical home pediatrician in carrying out these guidelines, and then look at how these can best be implemented.

And it just so happened that the AAP had embarked just a few months in advance of this project in revising their guidelines that were published in 2001, so this project dovetailed onto the AAP's efforts to update the guidelines for pediatricians. Those guidelines, I'm happy to say, before I came on the plane here, were just submitted to the copy editor, and they have been through four of the five levels of review from the Committee on Children with Disabilities, the American Academy of Pediatrics Autism Expert Panel; then all of the committees within the Academy that have anything to do with children with autism, school committees, community pediatrics, all of these different ones; then the last tier of review were outside reviewers. This

is where the Catherine Lords, Fred Volkmars, Amy Weatherbys from various other institutes outside of the pediatrics had a chance to review.

So all of those comments and recommendations have been incorporated, and this has formed and become the guideline for the medical home/primary-care that we are about to present. Now I believe that you have the entire handout. I think this is in everybody's packet or is available to people. This is our document. It is quite lengthy. There's no way to cover all of these recommendations in 15 or 20 minutes, but I kind of wanted to orient you to your handout.

This first column is actually the recommendations that are being made by all of these institutes, the American Academy of Pediatrics, and our workgroup. They are in agreement with each other from the different organizations. In fact, many of the people developing these guidelines actually overlap on these committees. As I said, these are close to being published within the next 5 or 6 months, hopefully. They still have one tier of review, and

that's the board, the board of directors for the AAP, and things could change. So that's why I'm saying this is a work in progress as far as the AAP guidelines.

The most important section is this middle section. This middle section is the actions that are needed by other entities in order to facilitate implementation of the autism guidelines in the primary-care/medical home practice. And the final list is somewhat incomplete compared to these two -- various resources, references, other guidelines.

There are five goals covered by these guidelines: One, general principles of medical home for the primary-care practice, and in particular, all of this relates to autism spectrum disorders. The second one is screening, surveillance screen, and the definitive diagnosis of autism spectrum disorders; the ongoing medical care after diagnosis looking at all of these -- medical, behavioral, mental health care, and complementary and alternative medicine. The fourth one is community services and coordination of

care, and the last one, transition.

Because of the time crunch, we decided that this would be the most important one to highlight, because it is the most radical -- the recommendations contained in this goal are the most radically different from the original guidelines of the AAP. They received the most comment from all of the different entities that have reviewed this, and they also might be the most difficult to implement. But I did, for completeness sake in the slides, just briefly touch on the other principles.

To lay the foundation, the whole idea of making sure that primary-care pediatricians know and understand the principles of medical home are encouraged to involve their entire staff in care of children with ASD, know that it's important to provide appropriate information to parents, especially value parents as partners and decision-makers and serve in a culturally competent manner.

What the pediatrician needs to do this includes various things, and this is the similar pattern throughout each goal and mainly as far as

funders, you know, being willing to reimburse the extra time that it does take to care for children with autism and providing maybe a portion of the cost for training and other things that we have recommended. And I'm not going to go through all these, because I do want to get to the screening and diagnosis.

But I will say we also want to put emphasis on our training programs, whether it be pediatrics, family practice, nurse practitioners, PA training systems, and helping them understand and buy into the importance of providing a medical home for children with autism and all of the extra things that go along with that when you're talking about children, not only with autism, but with any disability.

The second goal is the goal of screening, surveillance, and definitive diagnosis. First of all, we wanted to dovetail, re-support, reaffirm that screening and surveillance activities should take place in all children at every well-child visit. You may or may not have seen a new policy just published in July of 2006 that provides an

algorithm and, for the first time, really charges primary-care practices to not only do surveillance at every well-child visit but to actually use a standardized tool at 9-, 18-, 24-, or 30-month well-child visits. This is different from what we've been proposing or going by in years past.

Now what's important about this statement that was published in July 2006 -- it was the first time that the American Academy actually came out and said that all children should be screened for autism at the 18-month visit. Now in our previous guidelines, we said it would be nice if children were screened, for all children -- not children just with concerns, just with delays, just with behavioral problems -- but every single child. As you might know, that brought about many comments and some controversy, but we stuck to our guns.

A little bit later, our autism expert panel and people on our workgroup said, you know, the AAP should have said screening on all children at 18 months and 24 months in order to catch those 30 percent or so that may regress after 18 months. The writing group would not go along with that, so

the Autism Expert Panel, along with support from the workgroup, have written a commentary to *Pediatrics* saying we feel it important to add the 24-month screen on all children.

What's about to be published, we hope, in the next few months is the autism policy statement. In that statement, we affirm regular developmental screening, but we also specifically state that children at the 9- and 12-month visits should go undergo some sort of autism screening surveillance. And at this point, we can't endorse, but we are suggesting possibly Amy Wetherby's tool for that, since there are no screening tests for children yet, though these are being developed, before 18 months. Then we are specifically saying that all children should be screened at 18 and 24 months and, of course, at any visit when a parent may raise the concern.

We are specifically highlighting the value and importance of screening younger siblings of children with autism and suggesting heightened surveillance and screening, educating parents about the increased risks in subsequent children.

And then as published in the *Autism A.L.A.R.M.* in 2004, this idea of simultaneous referral and not waiting for the definitive diagnosis of autism, so, when a PCP, when a medical home/PCP suspects autism or some other developmental disability actually, we are telling them to refer right away, immediately, to either the early-intervention program if less than 3 years or special ed if greater than 3 years, to a local subspecialist are better a team -- but we realize that autism teams are not available in every community to help with the confirmation of the autism diagnosis -- to audiology and to local family support groups, including autism-specific ones.

And then the last goal is indicators for etiological lab investigation.

What I would like to concentrate -- let me just say in years past, what's happened is the doctor may refer to a subspecialist for a confirmation of autism, and months may pass. We determined that the average wait time for a child to be seen by an autism team is about 6 months,

and in some places as much as a year. So we wanted pediatricians to get the message to refer to early intervention. Even if the intervention is somewhat generic, it could be helpful. And not only that, many intervention people are very sensitive to signs and symptoms of autism. And, hopefully, individualizing their intervention plan will address some of the symptoms and characteristics of autism.

What does the pediatrician need to carry this out? Let me just say that the level of screening that we've suggested, not only for general development but in addition for autism screening on every single child at 18 and 24 months, is a burden in a sense of time, effort, and funding, so we felt like this is not going to happen unless professional accreditation understands that screening is important and endorses it and seta it as a standard, that training programs train the residents and physician extenders, professional organizations help PCPs and CME training develop innovative approaches to screening and surveillance, and that we have enough subspecialty

clinics available that appointments are available for confirmations of diagnosis so that children don't wait any more than 1 month. And you can see that all of these are quite ambitious.

As far as the screening and the funders, we need funders to reimburse the medical homes for the extra time needed to conduct surveillance and screening and to pay when more than one screen is recommended, because sometimes we're asking pediatricians to screen for general development as well as an autism-specific tool; funding physician extenders to help with this screening; the heightened screening in the siblings; more funding for an interdisciplinary approach to the definitive diagnosis.

And we need more intervention programs. I mean, what is the purpose of screening early, diagnosing early, if we don't have intervention programs that are effective and well-staffed and funded and specialists to help do the training? I just wanted to illustrate one point. This is an email that came to me. As I said, we had four tiers of reviewers, and this came from somebody

high up in the Academy leadership who reviewed our guideline and saw that we were asking for pediatricians to screen with general developmental tools and now, for the first time in history, with an autism-specific tool. And here's his point -- some are telling us that insurance companies will only pay one screening code per visit. I believe it should be billed and paid, too, at the 18-month visit -- and this is before the 24-month visit got in -- once for developmental screening and once for autism screening. If offices only get paid one time per visit, this reality could be used as an argument for the M-CHAT at 15 months and 24 months, though it seems crass to use payment as an indicator of a time of service rather than developmental imperative.

And for those of you that are familiar with the M-CHAT, it was normed and validated on 18-month-olds. So to say, oh, we can't get paid for both screens, let's just kick the M-CHAT up to 15 months and this would definitely change its value, its validity, and we would end up with many false positives. So it's just an illustration of the

barriers that pediatricians are facing as we lay onto them more and more guidelines regarding screening for autism.

I wanted to go on to the next one, which is ongoing medical care after diagnosis. There are many of these guidelines, and I certainly don't have time to go through all of them, but I wanted to highlight three of them. We're talking to the primary-care pediatrician. Do not abandon the child once the diagnosis is made. I'm from San Antonio, and in the recent months, I now average 25 referrals, not for diagnosis but simply to provide a medical home for children with autism, and I -- I'm not a primary-care provider. But pediatricians are frightened. They're overwhelmed. It may be issues dealing with immunizations with the parents. It may be issues of behavioral problems in a clinical situation and not being able to do the physical exam that you're so used to doing and not being able to come up with innovative ways of dealing with medical problems or the issue of parents being very in tune with alternative therapies and the pediatrician not

really being aware himself and feeling inadequate in the care of children with autism.

Another important point is access to community services and the importance of pediatricians knowing that there may be underlying medical causes of maladaptive behavior, the importance of not writing off maladaptive behavior to autism and the importance of looking for all those medical other entities.

I'm not going to go through what the PCP needs, but you can see a trend here. You know a trend? We need funding to help provide the more complex care that these children require. We need community supports to help us in our care for the family of children with autism, government to increase resource capacity.

The fourth guideline -- the first one was principles of medical home; the second one was the screening, surveillance, and diagnosis; the third one was ongoing care; and now the fourth one, community services and coordination of care. And I know that I'm speaking to the choir here on all of these issues, but they are all very important

issues to also address the collaboration, not only with medical providers but also other health care providers and the educational and social service systems and to achieve an integrated system of social services.

And finally, the fifth one -- transition. Transition has been high visibility for a long time. We all know of the many barriers to transition, and they are quite the same for autism, with a few individual differences, as they are with other children with disabilities.

So in conclusion, what are we -- what have we just worked on for this past year and a half. Well, number one, we've worked on guidelines that address the optimal care of children with autism, but these pose a significant change in pediatrician behavior right now given the constraints of funding, the lack of training, the lack of time, and the lack of reimbursement as we saw with our recommendation to do two screens, at the 18-month and 24-month visits.

And a second conclusion is that implementation of these guidelines in the pediatric medical

home/primary-care practice for children with autism or any child with disabilities, actually, can only take place and be possible with the support of professional organizations; public and private funders; Federal, State and local governments; early-intervention and education systems; and community agencies.

So what are our next steps? Well, I think that this document that you have in front of you, that I think is now almost 20 pages long, is almost ready to send out for broader input from stakeholders. We would like to pilot these guidelines with medical home practices through the Medical Home Autism Initiative in conjunction with AAP and other organizations.

These guidelines or a summary of these guidelines will be included in the autism toolkit, which I failed to mention. I mentioned that the first policy statement from the Academy of Pediatrics on autism was published in 2001. It was the policy statement and technical report. We felt that in order to implement this revised policy statement that hopefully will be published in July

of 2007, that we should provide pediatricians with a toolkit. Right now we're seeking funding for that so every pediatrician will receive a toolkit. At this point, we have funding for only 500 pediatricians, a sample of pediatricians to receive the toolkit.

That toolkit also has five layers of review, and it's on its fourth tier. It has just recently gone out to outside reviewers. These are people, professionals in the field of autism, parents -- there have been parent focus groups looking at the toolkit, but it is now up to about 75 tools. That includes screening tools, surveillance tools, algorithms for pediatricians, handouts for parents, websites, information on vaccines, a number of things that pediatricians have come to us and asked for help with. So these guidelines will also be included in that toolkit.

So, I think with 2 minutes left -- we are looking for input from you all regarding focus groups and how to get the information out and how to get comments back.

Dr. Insel: Thank you very much, Chris. We

actually don't have the full report, the 20-page report, in our booklets just because of a snag in getting these things printed. It will be posted on the website, and we'll be distributing that electronically to all of the Committee members very quickly so everyone will have an opportunity to see the fully report. We do have all of your slides, so there's a chance to go through in writing what you've just presented.

Time for comments and questions. Lee?

Mr. Lee Grossman: This is truly excellent. I appreciate the work that you put into this. This is long overdue and certainly a tremendous forward in the right direction. I have a long list of questions here, and obviously I'm not going to be able to get to any of them. But there are two that I will try and address here, and one of which is we've, at ASA, we have active an dialog going with some other professional organizations as well along these same issues, and has there been collaboration with the psychiatric and psychologists in developing these programs? That's my first question.

And the other one is you presented a number of issues here that certainly all need to be addressed and I guess it all boils down to what is your experience. What are the pediatricians telling you from the field in terms of their exposure and what -- how real to them is this epidemic of autism?

Dr. Johnson: I will tell you, in writing the first policy statement and the second and reviewing the literature, I think that autism is very much in the forefront. Various talks at the AAP, various talks – grand-round talks locally, when it's an autism topic, there's standing room only, which it is not for other topics. So I think they're aware of it. A survey that was done in New England, compared to a survey 5 years ago that showed most pediatricians will have perhaps a child with autism in their practice, the newest survey from New England published just a few months ago showed that over 50 percent of pediatricians had 10 or more children in their practice. So that was quite a bit of an eye opener.

As far as the -- the whole purpose of both the original developmental surveillance and now the autism-specific and to have those dovetailing each other was to raise the awareness of pediatricians. And that's our whole goal. In the Academy of Pediatrics, that's our whole goal -- is to help pediatricians realize not only that autism is common but that autism can be detected or at least suspected in the young child, because right now they're waiting for speech delay, which means that nothing even gets thought of until after 2 years of age. So we're trying to raise awareness.

I think Dr. Insel mentioned the pamphlet that we published 2 years ago -- "Is Your One-Year-Old Child Communicating With You?", we have been promoting that, not as an autism tool -- we didn't want autism on -- but we're promoting that as something to distribute to all families at their 1-year-old checkup. And when you read it, it's all about autism, but we didn't want to scare families -- does your child have -- does your 1-year-old have autism? So we're trying to raise awareness that way.

In 2001 -- the Academy of Pediatrics had no stand-alone autism seminars, lectures, whatever at their programs until 2001. Now in 2006 there are multiple autism opportunities at these conferences.

As far as review, the other professional organizations received the document at the fourth tier. So after each tier, we make revisions. So they should have -- I know ASHA -- you know, all of them should have. I know we did receive some comments from psychologists. Often what we the Academy does is send it to the president of whatever the organization is, and it gets funneled down to whomever they delegate. So I cannot tell you as far as psychology, which one, but we have psychologists on our panel, and they've seen these guidelines. And these guidelines, from the workgroup, are exactly parallel to the AAP. Any other questions?

Dr. Insel: Comments?

Dr. Zeph: Just I was wondering if there has been any interaction with the family practice physicians?

Dr. Johnson: Our guidelines here specifically mention family practice, and we are trying -- we have invited a family practice leader from their professional organization to be a liaison with our Committee. We are trying to invade the family practice. I know I speak for a national family practice. In the past, it's always been ADHD, and now it's always autism. That's what they want to hear about.

But, formally, we hope to, and in fact, one of our goals is to have a special mail-out to family practice practitioners of the autism guideline and some funding to send it to family practice residency trainee/trainer chairs so that they will have the toolkit also in the family practice residency programs. And we're hoping for funding with that and also linking them to our website that addresses autism, the policy statements, and we'll have the toolkit on the website.

Dr. Zeph: Will you be encouraging them to accept the guidelines?

Dr. Johnson: Yes.

Dr. Zeph: Okay. Good. Thank you.

Dr. Insel: Gail?

Dr. Gail Houle: My question was along the same line, and thank you. This is really good work. As far as getting the guidelines actually into practice, do you have any strategies that you think will be successful in that effort?

Dr. Johnson: Well, there is a subcommittee of -- well, I can talk mainly to the screening and surveillance, because that seems to have the most number of barriers, and there is a subcommittee on our committee, who's working on coding, trying to get things coded. And I am sad, too, that whether or not guidelines are implemented, especially when it comes to specific things like surveillance tools and coding tools that these depend on coding and funding. But I'm told that's reality. To me, it's a good thing, and it should be done regardless of funding, but that's not going to happen. So that is one of our biggest barriers, and they have developed codes. They have developed strategies where two screening tools can be funded, but oftentimes, it's at the State's discretion as to whether they will do that.

I went to a meeting, and one State was doing it beautifully. I came back to Texas and said this is how you do it, it can be done, and, you know, bam, bam, bam. In Texas, we don't do things that way. So I think that is a big barrier and I may be wrong, and certainly, Dr. McPherson or Bonnie or somebody can tell me, but I was hoping that, you know, this group at large would help with the implementation, with those things that pediatricians can't do. They can do the footwork.

They can be in the trenches seeing the children, but unless they're supported by funders and government and education and community, it's not going to get implemented, and there are steps that we need to take in order for this to happen. And that's why that middle column and our document are so important. It's what the pediatrician needs from the world, the USA health care/educational systems, human service systems in order to make this work. Yes?

Dr. Clara Lajonchere: I just wanted to touch upon a point we had made earlier. My name is Clara Lajonchere, and I’m from Cure Autism Now, and that

is a special collaboration. Cure Autism Now has a program currently, the Autism Treatment Network, that's doing a very similar thing, very parallel to what you folks are doing, and I just want everyone to be mindful that we're very happy to talk about working together in the file to advance the position. Because I think it is a wonderful initiative. Lee and I have been talking about how to collaborate amongst the activist organizations, so I just wanted you to know.

Dr. Johnson: Right. And actually, our efforts started prior to the meeting that you all had in Chicago. I attended that, and several members of this workgroup attended that. Jim Perrin -- I brought it to his attention that the Academy was already working on guidelines, so I'm well aware that you all are, too, and we added Jim Perrin to our review list. So he received a copy. Actually, he was part of our workgroup in the early days. And he's been with us all along. So has Margaret.

She's been real important with the Autism Treatment Network, too. So we were kind of relying on those folks who have close ties to you to

identify any problems or discrepancies and --

Dr. Insel: I want to just follow up on that, because I had the same thought. It might be worth, as you begin to think about the implementation of this, that you find a way to link. Clearly, one of the barriers, as you mentioned, is going to be what happens after referral. If it's 6 months to a year, that's actually getting out of the window where you want to be -- you want it to be more like 6 days to a month.

Dr. Johnson: Right.

Dr. Insel: And so what the ATN program is doing is to build this national network of specialty centers that could become a very important player for you for the pediatrics community. So it may be very important as you begin to develop this that actually as part of the platform that goes out is part of that toolkit that people become aware of all of those resources that are being set up currently.

Dr. Johnson: And you're exactly right. However, in Texas, a huge State, as of this date, we only have two or three possibilities for a team

evaluation, and our goal, yes, would be to have these resources. But the fact is that these resources are not available in many communities, and that's one of the big things that we do emphasize, that we do need access to the interdisciplinary approach not only to diagnosis but also to management.

Dr. Insel: It's just not there in many places.

Dr. Johnson: Right.

Dr. Insel: So that's a sort of secondary challenge that, even if this were working perfectly and everything were out there and everybody was doing the screening, it's not clear where those children and families would go in many places.

Dr. Johnson: Right. And I may have led you a bit astray in concentrating on the screening goal, but goal number three was the comprehensive care.

Dr. Insel: Right.

Dr. Johnson: In fact, that was the longest one, and we go into quite a bit of detail. And we do mention PAN and ATN and all of those other entities that are striving toward a coordinated

approach to care.

Dr. Insel: So we're out of time, but I had two quick questions. I hope just to finish this up by getting clarification on two things: One is, and this is sort of a follow-up to what Gail was asking, can you give us a sense of what the impact is of putting guidelines out there or what can we expect? Will there be pickup and implementation of this, or is this mostly just a process?

Dr. Johnson: This has been a huge concern for the AAP, because the 2001 guidelines, after publication of the 2001 guidelines, other than training and isolated practices starting to screen for autism, it certainly didn't catch on. And that's why the AAP convened the Autism Expert Panel, and our goal was how do you implement the 2001 guidelines? That was a little hazy on the screening. You know, we said it would be nice if all children screened, but we never really came out, because that was so radical back then. Well, what the autism expert group came out with was the Autism A.L.A.R.M. that went out to every pediatrician and said, you know, 1 in 166, and

that kind of opened people's eyes. I got all kinds of calls on that -- and wow, we must be missing them. You know? And then the brochure and then a booklet on autism that was sent out, a booklet to all pediatricians. And this was a 50-page booklet that the panel did to educate pediatricians.

Now that was, you know, 3 years after the fact. Now we have the new guidelines, and what we learned from the ADHD guidelines, attention deficit hyperactivity disorder, what we've learned from those guidelines that came out around 2003, I think, is that those are being implemented more consistently throughout the United States and in family practice. And the reason for that is they received funding for a toolkit. So they not only gave them the guidelines, but they said here's some tools in order to implement these guidelines. And the jury is not quite in. You know, it's still a bit out, but we think the toolkit is what really made the difference. And that is why we have gone through all of the effort to dovetail the toolkit onto these guidelines.

Dr. Insel: So that suggests that there may be

people even around the table who represent groups that may be helpful in this as well. One thought might be that as this gets put together in its final form, minus the toolkit, whether that actually is something you want to make broadly available to families as well who have autistic kids so that they can get it to their pediatrician in case this is a pediatrician who hasn't responded, issues like that that some of the folks here might help you think about.

And that's my last question, which is you had said in one of the slides that you're at the stage now of going to stakeholders and getting input from the community. But it wasn't clear how people do that. Is there -- what is the web address, or how does one make comments about the guidelines and their current state?

Dr. Johnson: I'm going to have to defer to the leaders as far as the --

Dr. Bonnie Strickland: Are you talking about the guideline that the workgroup is developing?

Dr. Insel: Right. So for where we are now, so if anybody -- because this has been such a quick

discussion, and I think there'll be people around the room who will probably want to weigh in on this, how can they comment on what's here.

Dr. Strickland: Well, if it's going to be on the IACC website, we could do it there, or they could -- I'll give you the website where -- we'll post them at our national center as well, and then we can pull them together.

Dr. Insel: Okay. Great, because I think it's a great idea to -- you mentioned town meetings and other methods of getting input, but certainly there's so many people who are major stakeholders in the room, and even from what you've shown, I think they'll have comments, probably a lot of them very, very positive. But it would be nice to have some place for them to respond. So that would be great.

Dr. Strickland: And I think that was one of the goals in presenting this, because we do want input.

Dr. Insel: Good.

Dr. Strickland: We do want to be collaborative. We definitely want to do that.

Dr. Insel: So we'll get an address in the course of the morning where people can respond and go from there, and we can also use the IACC website as well, but it may be better to go directly. Okay. Thank you very much, Chris. That was terrific.

We skipped introductions, and we skipped the normal sort of round robin. I think given the time, let's just jump into that. We've got a list of Federal partners here at the table. And as we've been doing the last few meetings, we'll just go around and get updates on progress. And I'll follow the list I have here, starting with HRSA, Health Resources and Services Administration, Bonnie, so that follows directly from what we've been hearing.

Dr. Strickland: Exactly. And I only have 5 minutes. Chris presented what HRSA and the Office on Disability have been supporting over the last 2 years. A little bit of background -- you've all probably seen this. This is a roadmap that the Services Subcommittee developed about a year and a half ago, and as a result of that, each of the

member agencies and entities on the Services Subcommittee had an assignment once that roadmap was developed. HRSA's assignment was the development of these guidelines for primary-care providers with, as you saw, the middle column delineating the kinds of support that primary-care practices need in order to implement what we expect from the medical home.

And that's the piece that we'll be looking for your input on. We've had the workgroup that's been working for a year and a half. We have finalized the draft. Our next step is to come to you and get your input on the entire package. I'm very sorry that we didn't have it here for you today, but I was really happy to see everybody digging around in their packet to see if they had it, because it means you were listening. So we will make sure that those are posted on the IACC website. We'll also post them, and I think they aren't yet, but we will post them at our National Medical Home Autism Initiative website at www.waisman.wisc.edu -- W-A-I-S-M-A-N dot wisc for Wisconsin dot edu. We'll compile them and synthesize them in

preparation for the next IACC meeting.

And I think I won't say any more than that. One thing I do want to say is that HRSA has no designated initiative or appropriation around autism, so we really are dependent upon partnerships with other entities such as CDC, CMS, SAMHSA and Department of Education, ASD. So I think we have to -- your point about partnership is not just important in terms of collaboration. It's important in terms of getting the support to move something like this forward. Whether it's service, training, or research, the bottom line is always how do you implement it, and I think that's where the rubber hits the road. It gets a little tedious, and I think Chris did an excellent job of talking about some of those issues.

I updated the group on the two national surveys that we support in conjunction with CDC at the last meeting, so I won't do that except to say that we're ready to launch the National Survey on Children's Health in early 2007. We can identify children with autism specifically through that survey, and this summer or early fall we will have

the second round of data from the National Survey of Children with Special Healthcare Needs, so we'll get some information on how the health care system impacts children and families with autism. Thank you.

Dr. Insel: Great. Thanks, Bonnie. Anything for Bonnie? Office on Disability, Merle?

Dr. Merle McPherson: I am currently detailed at the Office on Disability, but I've stayed in close contact with MCHB on the development of these guidelines, and MCH has an enormous history on developing clinical and professional guidelines and supporting that. This is very unique in that we have attempted to link it to the system's change activities that are required in order to get the kind of care we're talking about, so we're very excited and interested in how do we move this forward.

The other thing I want to say is that we, too, have no designated or specific activities in the Office on Disability for autism; there's no autism-defined money. But we are using the same roadmap framework for all of our national and

international activities that we're currently doing at the Office on Disability, which are intended to develop and support the generic system of care for all these children, which would be inclusive of children with autism and allows us, therefore, to link this roadmap with the broader roadmaps that are both national and international. And that's all I think I'll say at this point in time.

We are doing an international congress 2 weeks from today on serving -- community systems of services for -- children, youth, and families with special health care needs. We have over 60 countries at this point joining us. I'm sure there's going to be some autism discussion during that meeting.

Dr. Insel: Okay. Thank you, Merle. CMS, Ellen Blackwell.

Ms. Ellen Blackwell: Okay. Thanks, Merle. Merle didn't mention that several of our departments and partners are participating in discussions surrounding the medical home. CMS is one of them, so we are working on this very hard,

in fact, together. I ran across some numbers yesterday that I'll just bring up briefly that I thought were kind of illustrative of a move in this country toward community-based care.

The '95 numbers that relate to Medicaid spending on long-term care -- we spent $50 billion dollars in 1995 on long-term care, $40 billion dollars in institutional care, and $4.6 billion dollars on home and community-based waivers. In 2005 these numbers essentially doubled. We spent $94 billion on long-term care, $60 billion on institutional care, and this is the one that really gets my attention, $23 billion dollars on home and community-based services, so I think that that shows that there is a movement in this country toward -- away, clearly, from institutional services and toward home and community-based services. And there's a huge focus in Medicaid and on serving people with autism, people with disabilities and older adults in the community.

As I've talked about before, the backbone of these services are the 1915(c) waivers. We are

currently operating 295 waivers in 48 States. We have 58 waivers pending. The waivers that target people with autism operate in Wisconsin, Indiana, Maryland, and Maine. We have a fairly new waiver in Colorado that is serving children with autism, and I don't have a lot of data yet. The waiver hasn't been operating long. We are also having discussions with a couple of States, Pennsylvania and New Mexico, to implement waivers for people with autism.

Again, Medicaid is a program where States approach us. We don't go to them. So we're just working with those States.

Today -- I have to mention this, because it's a big day for us -- is the kickoff for our electronic-based 1915(c) waiver application. In the past, States have had to submit these huge documents to us, so we're really excited that states can put them in electronically, and this will make a -- it's been an enormous effort, so.

The last time I was here, I talked about the Deficit Reduction Act. Many of the other agencies have been impacted by this Act, and the Congress

built into the Act some new authorities that will help people with disabilities, including people with autism, and really build on the success of these home and community-based (c) waivers. Now that we've had a little bit of experience with them, and I mean a very little bit, I'm just going to touch on the ones that I think are really the most important to this group.

The benchmark coverage -- it's Section 6044 of the Act -- this is an authority where States can come in and actually target groups and provide specific coverage to them. We've approved four of these State plans in West Virginia, Kentucky, Idaho, and Kansas. I can't really comment too much about them. They're very new to us. We approve them very quickly. You can visit them online at our website. I would urge you to take a look. Kentucky has some things in its State plan that are targeted toward people with autism. Again, we don't have a lot of experience with this.

The Family Opportunity Act -- Section 6062 -- we're getting ready to issue guidance on this provision. It allows families that reach a certain

income level, 300 percent of the Federal poverty line, to purchase Medicaid coverage. And States can elect to add this to their State plans as early as January 1st, 2007. We haven't received any applications from States yet, but we expect to. I believe the coverage covers children ages 6 to 18.

Another provision of the Act that we're starting to gear up on, and I've talked about this one before, is a demonstration project that allows States to provide services to children who would typically be in institutional psychiatric facilities. We received 17 applications from States, and we hope to issue the grant awards by the year's end. That's 10 States, $218 million dollars.

Another section of the DRA that we've been working very hard in is what we call the money follows the person rebalancing demonstration. This is a huge project -- $1.75 billion dollars, a 5-year demonstration, and the goal of the demonstration is to take people out of institutions and put them into the community.

We've had a lot of interests from States. We released this solicitation in July. We received 38 proposals that we counted on November 1st, and we hope to issue these awards by early January. The vehicle for implementing this program is actually the 1915(c) waiver, so the division where I work is expecting to get a lot of work as an offset of this. The deal for States is that they get what we call an enhanced match. Instead of their regular -- it's generally about 50-50. Some States get up to about 80-percent match from the Federal Government, but States get an enhanced match when they transition a person out of an institutional setting into a community setting. So that's kind of interesting.

The program that I work, the (c) waiver program, is also going to be implementing the provision of the DRA. It's Section 1915(i). One of the big complaints about the (c) waivers has always been that to participate, people have to meet an institutional level of care. So the Congress, in its wisdom, decided to add this provision that would allow States to put these

programs which typically have to be renewed every 5 years directly into the State plan so that the States could continue their operation. They sort of did that, but they forget something or, you know, I'm never quite sure what the rationale is, but one of the issues with this particular provision is that States can't target people as they can with the (c) waiver. So typically, in a (c) waiver, as I said, you could serve people with autism, people with mental retardation or IAD.

Unfortunately, with this provision, States can serve people with chronic mental illness because the Congress added these services specifically. They also limited the services to nine statutory services. They didn't include the other services that we use in the (c) waivers that are very important to providing a comprehensive package to people.

So we don't have any applications from States. We've been working with one State that submitted a draft, and I'm working with another State that is probably in the next 2 weeks getting ready to submit a proposal that will provide adult day

health services. A couple of the services are targeted to people just by their very nature. Adult day health, for example, is not a service that would be delivered to kids. But we're sort of struggling with this benefit.

The last one that I think is pretty exciting is Section 6087, which is Section 1915(j). The Department and CMS are very interested in self-direction of care, people directing their own services, parents able to hire their children's providers. This section allows for -- and I have to be -- I'm going to be very specific about how I read this (reading): "Self-directed personal care and related services and home and community-based services" [end reading]. The Congress actually included all of the home- and community-based services in this provision that it didn't include in the "other" provision, but you have to get -- self-directed personal care has to be a benefit that's already in the State plan.

We haven't issued guidance on either 1915(i) or 1915(j). States can implement the provision as early as January. And as I said, we have a couple

of States that are getting ready to work with us on the home and community-based State plan services. We don't have anyone -- any States -- that have indicated an immediate interest in providing self-directed personal care through the (j) authority.

They can also provide it through the (i) authority. There are actually two separate places in the new statute. Again, I don't know the reason for these things. But it's a really good benefit, and it's going to be very interesting to see what happens over the next year as States start to figure these things out.

The National Association of State Medicaid Directors met in Washington this week. One of the topics on the agenda was all these various provisions and a lot of discussion about how States are going to be using them. There was a discussion about the medical home concept at NASMD.

I also wanted to mention that we are working with our contractor. I've talked before about our intent to provide guidance on promising practices

that States are using that deal specifically with children and adults with autism. I think we will probably release a paper by the end of the year. Our contractor is getting ready to start writing it. As far as our grant programs go, there's nothing really new.

I did see something this week that came about as part of our direct service worker demonstration, and it's not directly related to autism, but we're very concerned about the shortage of workers who work with people that have disabilities and older adults. And you should probably take a -- if you want to -- take a look at the website. It's at www.dswresourcecenter.org. We are awarding grants, I believe, through 2010 to look at how States can help encourage training and proliferation of these particular providers. Our other grant programs are still operating the Real Choice Systems Change Grants that help people stay in the community, the Ticket to Work Grants.

And then last but not least, Dr. Insel, I wanted to mention to you that I have data on autism from Medicaid. We're not ready to present

it yet, but I did hound and chase after our research people, and we have been able to collect some data on autism in Medicaid. One of the issues is that physicians don't always code autism as the primary diagnosis. If they see a child, for example, with a sore throat, autism isn't getting put on that sheet. But we do have some data, and we hope to be looking at it. We're working with our CDC partners to try to figure out what it means.

We also financed a 10-year study with one of our contractors. It's called the Medicaid Home and Community Based Services for Older People and Persons with Physical Disabilities Service Use and Expenditure Study. And I did manage to get the contractor to pull out some data on people with autism. The study is not ready for release yet. It's only been 10 years. Okay? But hopefully in the next few months, we should be seeing it. I've seen the data on autism, and I think it'll be really good. And, hopefully, maybe when we come back at the next meeting, we'll have some sort of cohesive presentation for you.

Dr. Insel: That would be extremely helpful. This comes up all the time. People are trying to understand what we're currently paying through Medicaid and now potentially Medicare for autism care. Can you just clarify a couple of numbers, because these numbers are mind-boggling.

Ms. Blackwell: Not to us.

Dr. Insel: You live in a different universe, a different fiscal universe. But if you are spending, or we I should say, are spending $60 billion dollars for institutional care and $23 billion dollars for home and community-based care -- were those the numbers?

Ms. Blackwell: In 2005, we spent $94.2 billion dollars on long-term care -- that's essentially facility nursing home care; $59.3 billion on institutional care; $22.7 billion on home and community-based waivers; and $12.2 billion dollars on regular State plan services. Medicaid spends about $300 billion dollars a year give or take a few billion.

Dr. Insel: Is there a way to break that down for children? Do we have a sense of what the

numbers would be?

Ms. Blackwell: I can go back and try to find out. I mean, I just ran across these yesterday, and I thought it was pretty interesting. I mean, I was mostly interested in the growth of the (c) waiver program. It was created by the Congress back in the early 80's as a demonstration project, and it really has truly become, you know, just one of the biggest parts of Medicaid. The hook is that States can apply to CMS. If it's going to cost less to provide care to a person in the community -- and generally it does cost less -- States would prefer to serve people in home and community-based settings. And they can cap the number of people that they serve. I mean, at the beginning, this was a very small program, but now it's huge.

Dr. Insel: I think if you spoke to people around the room, you might hear some concerns about the (c) waiver program that provides this enhanced incentive.

Ms. Blackwell: Well, that's a grant program, and it's time limited. It's only 5 years.

Dr. Insel: Okay.

Ms. Blackwell: And the enhanced match was meant to help encourage States. They just get it the first year when a person leaves the institution to try to encourage them to deinstitutionalize people and put them in community-based settings.

Dr. Insel: What we've learned over the last 40 years in mental health care is that that's a great idea as long as you've got the community resources there, but particularly in this area, I mean it's going to be a challenge.

Ms. Blackwell: I totally agree, and I would have to caution that the (c) waivers have never been a vehicle that's been very useful for serving people with mental illness because of the institutional level of care requirement. We only have, I think, I want to say, three or four waivers that serve people with mental illness. So one of the things that we think might be possible with this new DRA authority, 1915(i), is that the Congress did identify services to people with mental illness. And as I said, we can't target, but there are these services that are aimed at

people with mental illness, so we think that it's possible. Again, I'm just speculating. To serve people, it might be that a State might effectively serve people with mental illness through the State plan, not through a waiver, by using this new authority.

Dr. Insel: Well, we'll need to move on, but I think it would be really interesting, I'm sure, for all of us to hear about the autism data, because this comes up over and over again. And it's going to be, I think, important for us to track that and to see if there's any way to follow it out whether the costs are going up or down over time and how those costs are actually being deployed. So this is extremely helpful, Ellen, and this is the kind of data that, you know, for this group, we actually don't get this kind of input very often. So very, very useful to be able to hear this, even if it's only twice a year.

Ms. Blackwell: Well, good. I had one very dedicated researcher that worked in our Office of Research and Development who worked with me despite terrible pressure to be working on other

things. I'm very grateful to her. Okay, Stuart.

Dr. Insel: Stuart, can we -- a brief comment?

Stuart: Yes. Ellen, what's CMS's policy about providing in-school autism services through the program?

Ms. Blackwell: That's kind of a complicated question. I mean, I can go back to --

Dr. Insel: Why don't we cover that later? --

Ms. Blackwell: -- Alright --

Dr. Insel: -- because it's an important question, but we'll get back, and you can do that offline. I want to move on so we don't get too far behind here. FDA is the next on the list. Kathy Carbone is not here. Let me just say in her absence -- I know last time, I'm afraid I embarrassed her by asking her what FDA was actually doing about autism, and she said she's not allowed to talk about it. But indeed, in the end of October, FDA did issue the first license for autism. In this case it was the drug Resperadol for aggression and impulsive behavior. I think that's the indication for autism. It's the first time that's happened. So it's a sign of

progress, and we've had further discussions with FDA about more that they could do in the realm of thinking about drug development for the core symptoms of autism. And the question that has come up is how they could make that a target for drug development. So there's a lot of interest there, and it's one that we hope to capitalize on over the next 6 months. Hopefully, we'll be able to get back to that in May. Ellen?

Ms. Blackwell: I was going to mention that, when we started looking at data, we did approach our partners at the FDA, because we were interested in seeing if maybe we could track autism prevalence by drugs. And, unfortunately, we can't identify any drugs that are used solely to treat people with autism, but we did try to go that route. We have really talented pharmacists in one of our research divisions. We had ideas, but it kind of went nowhere, unfortunately. So if there's ever that drug, we'll be able to find that data for you, too.

Dr. Insel: Well, we'll look forward to that. NIH, Sue Swedo?

Dr. Sue Swedo: Good morning. I'll start with the programs that are moving toward their completion, and that's the STAART and CPEA networks. They just held their annual meeting last week, and it was really quite remarkable to see the amount of progress that had been made, particularly in the 10 years that the CPEAs have been in existence as they come to the end of their grant cycle. They're actually planning to publish a summary of their research accomplishments in a special issue of the *Journal of Autism and Developmental Disorders*.

The STAART Centers Network has about a year left, a little more than a year, year and a half. So they're continuing to progress and continuing actually to talk about new projects that they might be doing together during that time, so they are not resting on their laurels. They're continuing to work really hard.

Similarly, the Baby Sibs Research Network Consortium, which is a product of both the STAART and the CPEAs, is continuing. They are looking at the infant siblings of children previously

diagnosed with autism, and they had their annual meeting last week sponsored with help from Autism Speaks as well as the Child Health Institute and concluded that their focus is appropriate in looking at diagnostic signs and symptoms that are present in these infant siblings that would help us to move that age of diagnosis down as young as possible. They're also interested in looking at recurrence rates in a population large enough to have some meaningful data.

Much attention has been put on the ACE Centers, the Autism Centers of Excellence. These are actually both centers and networks. The NIH was very, very pleased with the number, the quality, and the variety of the applications that were received for the centers and networks. It was almost overwhelming, but not quite, thanks to the efforts -- of the efforts -- of the Child Health Institute's review staff, and certainly Alison and the other folks over there would deserve a huge debt of thanks.

There was good diversity of the topics of interest. We had hoped to have applications in all

areas related to the research matrix, and indeed we did as well as the geographic distribution. The reviews were held at the end of October for the networks and last week for the centers. The scores are known to the investigators. There will be another level of review by the program staff to make sure that those that are recommended for funding continue to represent that diversity of scientific and geographic distribution. So we should know about that at the January councils, and the first group of ACEs will be funded in spring of 2007. The rest of the ACEs would come on line then in the fall of 2007.

To support that effort, the National Database for Autism Research, NDAR, is being developed, and we're going to see a demonstration later this morning that I hope you'll find as exciting as we did. So I'll just report that we are engaged in discussions currently with the publishing companies that own the copyrights for the assessment measures that are so crucial to the common assessments that will really form the core of NDAR. And we've had some good positive

responses back from those publishing houses, so we're encouraged by that.

We're also working on data sharing policies. It's very clear that we need to let the investigators know before they enter into their negotiations what we expect from them in terms of data sharing and plan to follow the general NIH guidelines and take our lead from the genetics efforts that are already underway.

NDAR is on track to allow beta testing in January and full support of the ACE Centers in April. So last May, I had reported some trepidation, and I'm very excited that, thanks to the efforts of Matt and John that you're going to hear from later and their team, they made up a lot of time and they're back on track.

The Phenome Project is one of, as you saw in the evaluation, the matrix that perhaps had too much prominence in the matrix, but it certainly has been something we've been paying attention to. We held a workshop at the end of October to address the issue of use of data from existing data sets like the STAART-CPEA shared data that's

currently housed at DMSA as well as ongoing large-scale studies -- the CHARGE, the CADRE, the Norway and Denmark epidemiologic studies, and the AGRE sample -- and to be able to merge those looking for subtypes or -- I actually started thinking of them more as syndromes -- within the autism spectrum in the hopes that by getting some homogeneity of the subjects, we'll be able to get closer to the etiology.

The conclusion of that workshop was that merging the data sets was indeed desirable. It was quite feasible. We didn't get into issues of cost and sort of logistics, so the question of how long will this take and how much is it going to cost is something that we're exploring currently.

The intramural research program that's been established on autism is now no longer new. We actually feel like we've hit the groove and are really feeling established. The subtyping and regression studies are both underway and recruiting on average one subject a week, so we're able to with that goal. We actually are aiming for trajectory of two kids per week in order to make

up some time from the past year.

The chelation study has been approved by the IRB. We are waiting currently for results of the metals analysis to make sure that the vitamins and the DMSA are both mercury free, and then we'll be getting our kids ready to go.

The minocycline and protocols are also open for enrollment, so that program is looking for staff. If anybody has some great names, I'd be happy to talk to you.

And the other new initiatives at the NIH -- we're going to hear from NIEHS later today about the gene-environment interaction, and I would say that and the ACEs are the two things that we're really focusing on for the next few months. Thank you.

Dr. Insel: Thanks, Sue. Comments or questions for Sue?

Mr. Jon Shestack: I just had one question. So as the CPEAs sort of sunset out and the STAARTs soon afterward, is there actually then a mandate to repurpose this data that's at DM-STAT and some of it isn't at DM-STAT, but how -- because it was

a -- it is really the -- that is the most tangible result of the investment and 10 years in it, and that is what must stay in our system. So how do we mandate that that happens?

Dr. Swedo: Thanks. Exactly, it has already been mandated, and the program staff are working very hard with the investigators. All of them have requests for carryover funds, for example, and contingent on that, as with actually the last 2 years of sort of grants, they have been -- I don't mean to imply that they're not cooperative, because they actually are extremely cooperative.

Mr. Shestack: But it's an effort to be cooperative.

Dr. Swedo: It's a big effort.

Mr. Shestack: I understand.

Dr. Swedo: And they talked actually at their annual meeting about what would be required, and it seems quite possible within the money and the personnel that they have, and they are deeply committed to making sure that this happens. I know we've had talks in the past about what happens from DM-STAT. Matt can speak to that issue more,

but it's -- that is the first data set to get imported into NDAR.

Mr. Shestack: Right. My other question was, was there perhaps any money left during the CPEAs when there wasn't the coordinated data center but there was money for data coordination? Is there money left over in this account that can be used to incentivize some of these people to actually get it done in a timely fashion, to make NDAR a little bit more powerful, a little bit more quicker?

Dr. Swedo: I don't know if we have new money for carrots, but we have the old money for sticks so --

Mr. Shestack: That's fine. Thank you.

Dr. Swedo: That was a little too blunt. I'm sorry, Jon.

Mr. Shestack: Very good. Thank you. Appreciate it.

Dr. Insel: Other? Lucille.

Dr. Zeph: Just a question. You talked about the comment assessments in the data sharing policies that will be incorporated into the ACEs.

Two questions -- one, we had talked at one point about a common intake protocol, and has that been established?

Dr. Swedo: And that's actually based on the experience at the STAART Centers. The STAART-CPEAs had a common measures portfolio. We have taken that, sort of updated it, modified it. We're actually currently working on the physical exam form, the family medical history form, and the personal medical history form to merge all of those into a useful document. And those will be -- that is the core of the ACEs. It was in the RFA, and it's in the expectation. I'm sure it'll be at the grant awards that go out.

Dr. Zeph: In the family history pieces as well, and my follow-up to that is, since this is an interagency committee, are we looking at some collaboration across agencies for appropriate adaption or adoption if possible, and adaptation if necessary, so that other grant programs and other service programs begin to collaborate and we have a little uniformity? I think that, you know, we have an opportunity here.

Dr. Swedo: I would certainly agree.

Dr. Insel: Yes. Let me respond to that. It's a really critical point, and time is of the essence because there are a lot of things just leaving the station. I was at the autism consortium meeting in Boston a couple of weeks ago. They did a retreat where they're going to be pushing out a whole series of studies, and they want to have one common set of measures for evaluation, ATN and CAN having the same discussion.

So the opportunity here is, I think, to come up with a uniform consensus battery for evaluation and for what you could call basic phenotyping, knowing that every group is going to do something more than that, but at least everybody is collecting the same data. Let's say it's head circumference, something as concrete as that. Everybody's doing it in the same way with the same measures and reporting it in the same way. And to lose that opportunity would be, I think, a huge mistake right now.

So that's part of why this NDAR effort is going ahead so quickly, because we feel like we

need to have some common platform with a common set of definitions.

Dr. Zeph: But has the discussion broadened to the other departments? Because my concern, whether it's CDC or even the Department of Education, if for IES, are we looking at those -- because you're right. Once the train is out of the station here, we're going to be backpedaling and the opportunity --

Dr. Swedo: -- The CDC has been very intimately involved with this. As we've been going along, the Centers for Disease Control has established some of the common measures that we're utilizing, so they're definitely on board.

Dr. Zeph: I understand they're on board, but in terms of their RFPs and their upfront agreements, the way ACEs have incorporated it into the carrot and stick, so to speak, are those being adopted in the same manner?

Dr. Coleen Boyle: I just want to say I'm speaking for CDC, and I actually think that in all of our grants now, we have to have that as contingent in the award process.

Dr. Insel: Okay. That's a critical point, and one that we want to stay in -- that's really why we're here, you know, is to make sure that best practices get adopted across all of the groups and that we're doing this in a coordinated way. So thank you. Department of Education, Gayle?

Dr. Houle: Thank you. This is a good morning for me, because I've been told that we have a request for applications that's published in the *Federal Register* this morning, so you're probably the first to hear about it. You may have remembered that we do fund the Professional Development in Autism Center, which is a collaborative initiative of about six sites -- training, technical assistance sites throughout the country -- and that Center is in its fifth year. Ilene Schwartz is the principal investigator, and the main grantee is the University of Washington.

Well, since that is ending this coming summer, we have announced a similar initiative with a few upgrades and changes, but we have announced in the *Federal Register* today, so I've been told -- I

haven't seen it actually, the Professional Development Center in Autism, RFA, 5 years, $1 million dollars a year collaborative. We're looking for collaborative projects similar to what we did before where we have geographic diversity, and we have diversity of input thinking and output in what's provided. They will be trying to maximize the funds that they have by training teams, teams regionally or statewide, kind of the training-the-trainer model and families will be a part of those teams definitely.

I'm looking at the announcement that went into the *Federal Register*, and it's a little bit different from 5 years ago in several aspects. One is that one of the requirements is that this new entity to be funded provides training activities that are consistent with and supportive of Federal activities for children with ASDs such as the Interagency Autism Coordinating Committee with the website for this Committee and other federally funded ASD-focused personnel training and technical assistance projects. So I was happy to see that. That coordination is in the *Federal*

Register, and the website for the fondly known IACC is in the website as well for anyone who plans to respond to that RFA.

So that's exciting news. It is going to close January 2nd, and if you have the opportunity to be part of a partnership that goes in on that grant, I would encourage anyone here to do so, or if you want to get together groups of potential applicants that you think would be good applicants for this.

I expect that we would have an award made by the time we meet again, which will be in May. So at that time, I might be able to take a few minutes and give you some handouts and some information about what this newly awarded Center will look like as well as update you once again on the new training and technical assistance grants that OSEP, the Office of Special Education, is funding to build the capacity for serving children with autism out there in the States and the local school districts.

On another note, one thing is that the RFA is available at our Department website, which is

www.ed.gov. And also on that website, you can find a schedule of our Assistant Secretary for Special Education and Rehab Services, John Hager, for his schedule, and he is going to be conducting sessions that roll out the IDEA Part B regulations as it was reauthorized recently. And these will be throughout the country, different sites a couple times a month. So if you look on our website, there may be an opportunity for you or for your organization to attend one of the regs rollout sites. And if you have any Q&As that you wanted to interact with Mr. Hager on, he would be available for that, and he is our Assistant Secretary.

We have a couple of new tools available. Everybody has a toolkit or two, and so do we. And we have a toolkit available for parents of children with disabilities in helping to understand the newly reauthorized IDEA and its regulations. And I believe that is available at our National Technical Assistance Parent Training Center, which is www.taalliance.org.

So that's the update, and perhaps at the next or a future meeting, if there's time on the

agenda, I could prepare and, in fact, my colleague, Celia, could, and we could give you kind of an overview of the current research-to-practice to training technical assistance initiatives for children with autism.

Dr. Insel: Questions, comments for Gail? No? I think there's one here, and then we'll --

Dr. Strickland: Thanks, Gail. That's great. I have a question about the RFA. It's a training. Training for whom? You mentioned teams. Might that also include community primary care practices, medical home, or is it primarily for --

Dr. Houle: -- Sure. No, it's not -- it's teams who have the capacity to then -- people come together, train teams who then have the capacity to make some changes and improvements in service delivery, so any -- you know, however the grantee wants to set it up, however they want to target it, there's no specification. It can include as many different providers as they feel will benefit and be able to get maximum leverage from the training.

Dr. Strickland: Great. Because I think by the

time these guidelines get reviewed, synthesized, and finalized, that might be right about the time that your award is made, so maybe there's an opportunity to work together there.

Dr. Houle: Yes. So they're definitely included, as are what we call professional developers. Some States and school systems have professional developers, and we thought one way to leverage would be to get to those people who could then spread the professional development training throughout their State, but medical practitioners are welcome as well.

Ms. Ann Gibbons: Yes, very brief. Thank you, Gail, for the work you're doing. We really appreciate it. I'm just wondering if there's precedent among disabilities for the Department of Education? Have you ever drafted and disseminated a direct best-practices publication for other disabilities, and if so, is that something you would consider for autism? Because those of us who deal with it every day know that our best and brightest hope for these individuals is the educational intervention at this point.

Dr. Houle: We don't have, like, a manualized best practice. One thing we did years ago, probably 5, 6 years ago now, was the National Academy of Science's study, which provided some guidelines, educating children with autism as to what the research says are components of an effective program for children with autism. But as far as manualizing an approach per se, we would not do that. Our guidelines, and we've always said this, for the implementation of any program for any child with disabilities are the IDEA statute and regulations. And then it's up to the States, as long as they comply with the IDEA statute and regulations, to get more specific about how they feel they can best meet the needs in their State. So States may issue guidelines, and as long as those guidelines are in accordance and don't violate the IDEA statute or regulations, then we wouldn't intervene in that way.

Part of it is that because education is such a State and local field of endeavor and it's locally funded and it's State funded, that other than the IDEA statute and regulations and every State

having to submit their plan to us for review to make sure that they comply with those, there's not a lot of support for the Department of Education to issue real specific guidelines or dictates for States or locals to follow. They really -- in Congress, there's a lot of opposition to that, and State people as well. So, you know, we --

Dr. Insel: Gail, I'm sorry to interrupt, but we just -- since we had from the American Academy of Pediatrics, and so they took that on as an agenda item, is there a kind of corollary to that? If a Federal agency isn't going to do it, is there some professional organization that could do something like this? I mean some of us know nothing about the educational role, so --

Dr. Houle: -- Any professional organization would be able to do that and circulate those to the field. There would be no Federal control or intervention on that.

Ms. Gibbons: And Tom's asking what would be the name of that organization --

Dr. Houle: Who wishes to take that one? I honestly don't know, being at the Federal

Government level, who would -- whether there's, you know, any autism advocacy organizations who would be interested in taking that on.

Ms. Gibbons: So the best we can nag you for is professional development grants essentially?

Dr. Houle: Well, I'm not sure you mean by the best that you can nag me -- we have professional development grants; we have technical assistance initiatives; we have billions of dollars that go to States, to locals, for the implementation of IDEA, so in terms of what's available --

Ms. Gibbons: -- Doesn't there need to be some evidence basis for what educational interventions would be used before you can have a consensus? I mean, it sounds to me like you want some sort of a consensus report and then dissemination of that, but doesn't -- I mean as an NIH-er, I'm thinking if you were going to have a psychiatric intervention or a pharmacological intervention, you would want some evidence base for that --

Dr. Insel: Some of that was put together in the IOM report in 2001, something like that. So there was an IOM study that looked at the evidence

base for educational interventions, but the impact of that still remains to be seen in terms of any sort of practical consequences. So there's a document out there that says this is what we would consider to be best practices in terms of educational practices.

Dr. Story Landis: So there is actually a summary which says what should be done.

Dr. Insel: Right. So what Ann is asking is, given that that's out there, what's been the attempt to do what we heard about from the American Academy of Pediatrics to actually say these are best practice guidelines that should be implemented in your community?

Dr. Landis: Couldn't that be tied to whether or not you got the money --

Dr. Houle: -- States have to develop --

Dr. Landis: So if there's a – [Inaudible comments]

Dr. Landis: -- but don't the States have to pay attention to this report?

Dr. Houle: States have a State plan that has to be reviewed in order to get the Federal money.

Dr. Insel: No, they don't --

[Inaudible comments]

Dr. Landis: -- So that doesn't make any sense at all, does it?

Dr. Insel: -- So the --

Dr. Landis: Sorry.

Dr. Houle: I don't know if you -- States have -- as far as the Department goes -- States have to comply with the IDEA and then the IDEA does have stipulations for evidence-based practice.

[Inaudible comments]

Dr. Insel: -- to be the last comment, and then we'll have to move on, but it will be explained for us, so we'll --

Ms. Ness: -- especially in early-childhood programs that Gail is among the people that oversees, States have to meet specific child outcomes. And the Department is working with States so that the interventions have to actually prove to be appropriate to the child and allow that child to meet a certain outcome. The same is true for the school-age programs. So it's -- I wish we were farther along than we are, but I

think the Department, in its role, is monitoring what States due, and trying to enforce the law is requiring the States to prove that what they're doing is actually being meaningful for kids. And one of the benchmarks for older kids is are they graduating with a real diploma and certain things like that. So I think you're seeing more specific child outcomes in the early-childhood programs, the birth to 5 programs that are specific to very specific child outcomes. And the Department's monitoring States on that. And I think it's a bigger process with the older kids. So it's coming. It's not as far along as I think any of us would like it to be, but it is coming. So the Department can't tell States what to do in a direct intervention, but they can say what you do has to be meaningful to specific outcomes for children.

Dr. Insel: Okay. I think we're going to have to move on, because I don't want to get too far behind.

Mr. Grossman: Can I ask a question?

Dr. Insel: Real quick.

Mr. Grossman: Okay. Ann, we've worked with the NEA on developing a document related to educating children with autism, and it's been widely disseminated. And it's probably one of the better instruments out there in terms of what standards should be employed. Also the book that Gail had referred to, *Educating Children with Autism* is an excellent resource for what is currently available in terms of evidence-based best practices and standards that are out there. And it addresses really the early intervention through probably 8-year-olds. And we also have a number of initiatives going on in terms of developing better educational standards for evidence-based work, and I believe in May, we'll have much more information to report on that.

Dr. Insel: Okay. We're going to have to move on, because we're falling behind. Patricia Morrissey just came in, Administration for Children and Families. We've been going around the room just getting updates from each agency, so welcome.

Dr. Patricia Morrissey: I think my job is talk

about emergency management? Is that correct, or is this a different part of the agenda? Okay. Great, I was asked to give an overview of a conference we had in June. It was the first of its kind, and the impact of that meeting, I think, is something that went way beyond our expectations. Several staff and myself went down to Louisiana, Mississippi, and Texas after Katrina last year, and the most obvious thing we learned, which was also reflected on television and other media coverage, was that people that should have been talking to each other after the disaster as well as before the disaster clearly weren't, and that was especially true with regard to people with disabilities and the elderly.

And the other thing we learned is, obviously, if these people didn't know each other before a disaster, you couldn't expect them to know to reach each other and help each other during a disaster or after a disaster.

So it was probably the most profound human experience that I had, because looking into the eyes of people that went through this, especially

parents with kids with very complicated disabilities, and seeing the expressions on their faces. It was just like a mind-altering or, you know, a body-altering experience. You wanted to help, and you didn't know what to do.

I also have been in this town since '76 so I went, “Well, I don't want to do something that will make us all feel good; I want to do something that will really have an impact.” So Secretary Leavitt and Secretary Chertoff agreed to request from governors to send delegations to Washington last June to basically work together to come up with plans for assisting people with disabilities and the elderly in any kind of an emergency. And governors were asked to appoint people from State-level emergency management, Homeland Security, health, mental health, special needs, and aging. And then, remember, because ADD underwrote a majority of the conference expenses, we asked that a person from our grantee network -- and we have 180 grantees across the country -- be a disability representative as part of the delegation. And the 45 States sent delegations.

And the objective was a simple one -- that these people would get to know each other and talk to each other. In the morning, they heard from experts with regard to the topic. We narrowed what we covered. For example, we covered things that were important to cover like what to do in an evacuation: Do you keep registries, or don't you keep registries? What should the response or recover aspect look like? What is the role of case management?

And in the afternoon, these delegations worked together both as a State delegation and as in a regional room, and they had access to experts that could provide them with information or answers to questions they may have as they were talking. And each State delegation developed for its governor basically some ideas that would be pursued when they went back home.

The interesting thing is we obligated these delegations to respond to us quarterly on what they are doing since that conference. And 35 of the 45 States actually did send us reports on October 1, which, to me, was miraculous, because

really there was no way -- you know, there was no reason for them to do it. What was reflected -- I would say 33 of the 35 clearly were engaged. Many were incorporated into larger State initiatives. Many were catalysts for State initiatives, and many had not only dealt with things that State-level people should be concerned about, but they, I think seven or nine, actually replicated our conference at the local level to have a larger impact. And so we're anticipating a few more quarterly reports. We have a website.

There's a set of slides in your handout that gives you much more detail about specific States and what we've learned from the initial reports. The most useful thing, though, I think is the website. The website is amazing. We have maintained a website before, during, and after the conference, and we will -- we have made a commitment to keep it going at least through June 30th of 2007.

The most interesting thing that I've learned is that now 30,000 local emergency management people are using that website as a resource to

deal with issues. So I think our interest in having an impact was verified by what we've observed in the last few months. And I'll be glad to answer any questions, but I think, as a strategy, if you all, no matter what the topic is you're interested in, whether it be medical research or something else, I think we accidentally came upon a process that can have an impact, and you might want to consider -- that's why I spent my time on the strategy.

Many of us go to conferences, and, you know, we're really inspired, and we go home with remembering a good taste of a great piece of cake, but we don't have a recipe of, you know, know to bake that cake. And I think what has happened is we've created something now that we have no control over, but it's definitely positive.

Now with regard to people with autism, I think there are two specific products I can mention. One, you can access through our website; the other one I'd have to track down. But there is something called TIS responders that one of our university centers developed. And it's a little laminated

booklet, and it's been updated, that emergency responders can wear on their belt, and it basically tells you how to interact with anybody with any kind of specific functional limitations, including people that communicate or people that might be disoriented or people that don't like a change in routine.

The second thing -- there is a communication board that was developed specifically for people with autism that was used in shelters. There are people who can point to pictures to say what they would like or want.

So any of you who have an interest in emergency management and that kind of thing, we are very invested, and we will company continue to be, and we want to be seen both as a resource and somebody that would get information to other people if you happen to come across it.

Dr. Insel: Thanks, Pat. Comments or questions? Lucille?

Dr. Zeph: I just wanted to comment that during the aftermath of the hurricanes, there were incredible stories around what happened to the

lives of people with autism, and the work that Pat has been doing on this, I think, is incredibly important. You know how disruptive it can be to the lives of families in general, but for families who have a family member with autism, some of the horror stories that we heard and the time that it will take to put those lives back together, is just phenomenal. And if there's anything that we can do on the prevention side of that to make life easier, I think is just so critical to families and for individuals with autism.

So as low incidences we hope these events are in the future, I think that the work that's being done to prepare and to raise the awareness of the public sector in the emergency preparedness area is really, really critical. And you don't -- there's no time to do it when you're in the situation and the devastation that happens working with our colleagues around the country in the UCED network that worked on this issue, the stories were really overwhelming. And I know that Pat went down and did firsthand experience with this, but the stories go on and on around families of kids

with autism in particular.

Dr. Insel: Okay. I think, given the time, rather than taking comments, because we're behind schedule, that all of the people around the table will be here through the day, so there'll be a chance to talk to them individually. And we better march on, or we're going to miss the chance for one-on-one conversations in the hallway, which I know are very productive here.

SAMHSA, the Substance Abuse and Mental Health Services Administration, Dr. Larke Huang, who represents that agency, will not be here until noon, but Elizabeth Lopez is here, so maybe you can get us up to day. Welcome.

Dr. Elizabeth Lopez: Thank you. And Larke sends her regrets for not being able to join you this morning. She had a competing engagement, but is looking forward to being with you for the afternoon. You may know that Larke is working as a senior advisor to our administrator at SAMHSA on children and families issues and is continuing the work that Sibyl Goldman began at SAMHSA as an advisor to Charlie Curie. And in her capacity as

well, Larke has been taking the lead for children and family issues at SAMHSA. She also is tasked with leading the agency on issues relating to seclusion and restraint and the elimination and reduction of that across the country in facilities and other nonmedical settings as well as serving as the principal lead for health disparities and improving and enhancing cultural competence across our agency.

And so as I'm listening to people's reports around the table this morning, I'm thinking what a wonderful opportunity for you to have Larke as part of this Committee as a liaison back to SAMHSA. I'm happy to say that a lot of our activities, again, while none of which are principally focused on autism or targeted to autism, a lot of our activities have vehicles where we can distribute and disseminate information to providers who very likely could be in contact with people who have autism and autism spectrum disorders. So I'm just putting that out on the table. I'm sure Larke will continue to talk with you about that.

She wanted me to alert you to two things that we're working on that this body may be interested in, and I'm sure she'll be happy to talk with you more specifically about it this afternoon. The first is, for those of you who may be familiar. SAMHSA has a national registry on evidence-based programs and practices, or more commonly known as NREPP. I always have to read the whole entire title, because I've only known it as NREPP. And we've been going through a revamping process, collaborating with our partners at the Institutes, and it's a voluntary rating and classification system really designed principally to provide the American public with reliable information on the scientific basis of interventions that prevent and/or treat mental and substance abuse disorders.

You may know that -- this has kind of been a developmental and iterative process at SAMHSA over the last several years and expanded out of our prevention activity at the Center for Substance Abuse Prevention, and we're kind of working to try and make this a tool or a decision-support tool that really has broader applicability. And we went

through a long process, 18-month process, of receiving public comment for how we can make this better, more available and also more user friendly and make it so that people are not feeling like the only kinds of programs that are available to them are programs that they don't have access to because they cost too much money or programs that don't meet their criteria that previous or earlier iteration that NREPP made that didn't include principally some programs that just couldn't possibly meet that level of criteria but were able to achieve certainly qualitative, if not quantitative, outcomes that were -- seemed to be -- positive.

So right now, we're at an open and public comment period for -- excuse me -- an open submission period for new programs that will be reviewed on the NREPP. And two major improvements to our new iteration of NREPP is that there'll be a searchable database for outcomes that you're looking for to improve in whatever your principal focus area is and also that once your program -- your program won't be labeled as model, promising.

Every program that meets the principal criteria will remain on the registry even if they don't measure up to kind of the standard of meeting complete high, you know, fidelity implementation model initiative but that public will have still at their disposal a listing of all the programs. So she wanted me to let you know about that, and she can talk to you more, I'm sure, about that this afternoon.

The second thing is that you may know about our Federal partners for mental health at our Center for Mental Health Services, Director Catherine Powers convening, and as a part of that partnership, many of our partners here today are participating on that executive steering committee. There's a series of subgroups or priorities of sub-workgroups, one of which is primary care and the integration of mental health and substance abuse services, and the Office of Disabilities represented there, several of our partners here, ACF, HRSA are also represented there. In fact, HRSA is chairing the subcommittee with SAMHSA from the Bureau of Primary Care. And

we're in the process of developing on that workgroup an overall plan to present to the Federal partners on the proposed integration of mental health and substance abuse services in various primary care contexts. And I think we see this as an opportunity for being able to bring into the spectrum of discussion services for children for all disabilities, including the principal disabilities that SAMHSA is moving forward, but all the disabilities that are represented around the table at our workgroup. So those are the two issues that she wanted us to update you on.

Dr. Insel: Okay. Thanks very much, Elizabeth, and Larke will be here, I think, at noon or soon thereafter. Anything for Elizabeth before we move on?

[No response]

Dr. Insel: Okay. The Institute of Education Sciences, Celia Rosenquist, is here.

Dr. Celia Rosenquist: I just wanted to give a brief background. Once again, our National Center for Special Education Research is the newest

within IES and was created with the reauthorization of IDEA, so we've only been in existence for about a year and a half. In 2006 the Center offered a grant program focused on ASD, and the purpose of the ASD research program is to identify, develop or modify, or establish the efficacy of comprehensive preschool and school-based interventions that improve the academic communication, social, and behavior outcomes of children identified with ASD in preschool through middle school.

Also, the purpose of the program is to develop and validate academic communication, social, and behavior measures, to monitor progress and evaluate outcomes for children identified with ASD in preschool through middle school.

The deadline to submit the applications was actually yesterday evening, and I think we're expecting approximately between 30 and 40 applications. The applications will be reviewed by our IES panels in February-March 2007, and the number funded will be determined by the significance and scientific rigor of the

applications. And I'm hoping by the next meeting, I'll be able to provide you with some information on the funded projects.

Dr. Insel: Okay. Thank you. Questions?

[No response]

Dr. Insel: Okay. The last but certainly not least partner here is CDC, and welcome to Coleen Boyle, who will be taking over in this position from Jose Cordero who has now retired.

Dr. Boyle: Well, official retired from the Federal Government, but he's now on to a new job and a new challenge, and most of you know he's the new Dean in the School of Public Health in Puerto Rico, and so he's going home and he's quite happy. but he's also jetlagged and jetting around, as Jose always does, from place to place, so hard to always keep track of him.

Dr. Insel: We're delighted to have you here.

Dr. Boyle: Well, thank you very much, and I'm delighted to be able to give you an update. I think we have some interesting things to report. And, again, I want to report on our three major activities, our epidemiology activities, our

surveillance activities, and then our health communication campaign that many of you heard about, the Learn the Signs. Act Early.

In terms of our epidemiology activities, the major focus for us has been in terms of trying to develop the CADRE program or the Centers for Autism and Developmental Disabilities Research and Epidemiology. And I know you have sort struggled with us as we've struggled to get funding for them, but I think we're on fairly sure ground now in terms of moving forward. We finished the first 5 years of funding for that program. In that program, we had three focuses. One was surveillance. The other one was a national collaborative study. And then we funded special studies on that. And many of those participants in that, they are going to be reporting on their surveillance data in the collective reports that I'm going to mention to you in my next update on the ADDM.

But the protocol for the CADRE study is complete and has been finalized, and it's now in OMB. So we've just re-competed and refunded those

Centers, and they have started their new cycle of funding in October of 2006. And we're essentially scaling back that project to really just focus on this national collaborative case-control study. And hopefully, once we get through OMB clearance, that project will be collecting information and enrolling families and children, hopefully in early 2007, but that's probably being a little bit optimistic for OMB clearance.

In terms of the next update, our ADDM Project, this is the Autism and Developmental Disabilities Monitoring Network; we've also funded a second round of grants for that project. That was started in 2006. For the first funding cycle, we actually have two reports that will be coming out in February of 2007, and they'll be published in CDC's *MMWR* surveillance summaries, and *MMWR* stands for *Morbidity and Mortality Weekly Report*, sort of a draconian title for it, but it's historical so we'll just say *MMWR*. But essentially, those two reports, the first one will be for six areas of the U.S., and that will be for the prevalence year 2000.

And then the second report is going to be an update of the prevalence for 14 areas within the United States. We are also working on -- eight of the sites are completing data collection analysis for the year 2004, and so we hope to report on the 2004 study year by the end of 2007.

So our hope here is to really accelerate the delivery of information about the prevalence of autism through this Network, now that the Network is well established.

I don't think I did say that in the second round of funding, we dropped back from 16 sites to 10 sites, and this was sort of our juggling around of our funding to be able to well-fund our CADRE program as well as to continue our surveillance activities. So we're looking forward, and hopefully in the next meeting, in May, we can do an update and maybe a more detailed update on the information coming out from the prevalence studies.

We also have a sort of a parallel activity that's starting to take some life, and that is trying to develop a method to determine prevalence

of autism in younger age populations, that is children under the age of 4, as well as we were hoping to try to actually do something similar for adolescent and young adult populations, but we haven't been so successful in that area yet. But we do have three 1-year developmental cooperative agreements with the Florida State University, the California State Health Department, and The University of Utah. And those 1-year cooperative agreements are really trying to develop the methodology to examine prevalence among very young children or children under age 4. And hopefully we're -- depending on the success of those programs -- our intent is to fund at least one of those programs to go forward and to develop surveillance capacity for young children.

I didn't mention, but with the ADDM program, our ongoing monitoring program, this includes children at age 8. We did have a 4-year-old component in the RFA, but I don't think we had the funding actually to be able to fund both the 8-year-old and the 4-year-old components, but Cathy Rice is here with me, and she can clarify that for

me.

And then the other thing I wanted to give you an update on -- we're very excited about -- is the Learn the Signs. Act Early. I know you've had several updates of that campaign over the years, but we're into its third and final phase. And this phase is going to be focusing on childcare providers, and actually it began with the launch of the campaign last week at the National Association for the Education of Young Children conference, the NAEYC conference, which actually was held in Atlanta, which was very fortunate for us in terms of travel-related issues. But obviously childcare providers are a very integral part of this whole issue of trying to identify children early who are impacted by this condition.

And to prepare for the launch of this component of the project, as we've done with the other two components, we've conducted interviews with childcare providers, really did the formative research with childcare providers and directors to try to get their insight in what the potential materials and messages would be in terms of trying

to get them to work in identifying children with developmental problems early. And I just wanted to go over some of the key findings from that work.

Really, familiarity with milestones and early warning signs of developmental problems vary tremendously among the groups of childcare providers and directors that we interviewed. They recognized their role in early identification and, really, the importance of early intervention. But with the exception of Head Start and Early Head Start, few providers had a plan in place to refer parents or knew of specialists in the area which they could refer children to. And one of the real challenges that they pointed out was that, you know, they needed materials, they needed training to be able to bridge that challenging or that very difficult conversation with parents in terms of talking to parents about issues of concern.

So, as with our other targeted components, we have developed a resource toolkit, as everybody else has had their toolkits, but this is a -- I've actually brought a copy along with me for those of you who would be interested in taking a look at

it. It really does provide the providers with the campaign messages, and it includes an interactive CDC -- excuse me, a CD-ROM, as well as a -- a little Freudian slip there -- as well as other resource tips for parents and childcare providers. So we're very excited about this campaign. It will be rolling out over the next year. Obviously, the NAEYC part of it was just the first launch, but we will be networking with major childcare providers and other organizations that involve caring for young children.

Dr. Insel: Great. Thank you. Comments or questions for Coleen? Lee?

Mr. Grossman: So the prevalence data, the first time it's going to be published is in the *Morbidity and Mortality* issue, so the AAP journals aren't going to be -- we've been hearing rumors that that was going to show up in some other journal, *Pediatrics*, et cetera?

Dr. Boyle: Yes. Well, what we decided to do since we were going to continually report on the prevalence, we wanted to find a venue where we could essentially put this information out

relatively quickly, so that's what we're going to do.

Mr. Grossman: Any -- can you spill the beans a little bit on what it looks like?

Dr. Boyle: Well, again, I'd be happy to provide an update next time and more detailed information.

Mr. Grossman: That was a real smooth answer.

Dr. Boyle: It was, yes.

Dr. Insel: One of the things that you'll hear, I think, this afternoon when we talk about the autism matrix and the evaluation was the need to go from prevalence to incidence data. Will any of this help us that way? Is there an opportunity to go to the same population with the same ratings over time?

Dr. Boyle: Well, prevalence and incidence is always a very challenging when you talk about a chronic condition like autism as with any disorder, even with a birth defect. We talk about birth prevalence, because essentially we can't really count incidence per se. But I think what you're trying to say is there's a way to capture

all children within a stable population over time, and some of the work that we're doing with the -- at least some of the developmental work that we're doing with the -- early-age surveillance will hopefully address some of that, because we'll be less likely to lose children through attrition in that ongoing monitoring.

Dr. Insel: So I'm just not sure exactly how this is set up, but if you go back to the CADRE sites, and what you were talking about is in February, we'd get reports on, in one case, 6 sites, and on the other case, 8 or 14. Are those the same sites that have been reported on in the past, or are these different sites than what we've heard about?

Dr. Boyle: The 2000 data and the 2002 and 2004, those are essentially cross-sections of the population for a specific location, so it's on a birth cohort approach, is essentially what we call a period prevalence approach. You know? So let's say in the population, what's the burden or what's the prevalence of autism at a specific point in time. So you can look at children who've moved in.

You can look at children who've moved out. And you can look at, you know, other issues to try to understand why that rate may change or not change.

Dr. Insel: And the data will be -- it's administrative data, or what's actually going into the data sets for prevalence?

Dr. Boyle: This is ADDM we're talking about. The CADRE is a totally different ball game. But for ADDM, it is an administrative prevalence, so it's children who are recognized either with autism or with another developmental concern that, based on -- we do a clinical review of the records as part of the ADDM program. So if a child is not necessarily diagnosed with autism but there's enough clinical information, you know, signs and symptoms that the clinical reviewers -- and they have a standardized way to evaluate and assess that -- can say that that child most likely has autism, then it's included in the case definition.

Dr. Insel: Okay. I think this will come up later, because I know that in the evaluation, there was a lot of discussion about the way forward on epidemiology and how to make the data

sets deeper in some ways.

This is the end of going around the table. Is there anything else to add from the group here, any other questions, concerns, discussion points? Lucille?

Dr. Zeph: I just would like to comment on Coleen's presentation. Coleen, I just really want to commend you on the work with the childcare providers. I think it's a really important complement to what's going on with the Academy, and that partnership will be really critical in the future. But I wonder if in terms of your dissemination through NAEYC -- that is a wonderful start -- I wonder if you have approached a UCEDD on this issue because the University Centers for Excellence in Developmental Disability might be a really good point of referral for many of these kids, and many of the Centers have technical assistance and other kinds of agreements with their ops of childcare and Head Start and childcare centers throughout their State. And since there are 67 of those in every State and territory, it may be a helpful way to consistently

work with that population, so --

Dr. Boyle: And that's an excellent point, and I was going to turn to my colleague, Katherine Lyon Daniel back there. I don't know if we've made contact with a UCEDD.

Dr. Katherine Lyon Daniel: Yes, we have, and we actually have awarded a UCEDD grant funding to hire a full-time medical fellow who will be joining us to do outreach for health care professionals and in this area as well. So we have a huge plan of outreach that Coleen couldn't summarize today, but you can find it on our website at www.cdc.gov/actearly.

Dr. Insel: Other comments?

[No response]

Great. Okay. So what we'll do now is let's take just a 10-minute break if we can, then reconvene at 10:50 to hear about NDAR, and we'll get into the science presentations at that point.

(Whereupon, a recess was taken from 10:33 a.m. until 11:48 a.m.)

Dr. Insel: If I can have you take your seats. We want to continue on the next session, and we

have a PlayStation 3 for anybody who's sitting down. We wanted you to hear about NDAR. Before we do that, let me just make one announcement. In line with what we were talking about in the previous session about some guidelines and toolkits, there is a new document out from the American Speech-Language-Hearing Association of evidence-based practices for speech pathologists that can be used in the treatment of autism spectrum disorders across the lifespan. This is a document that has gone through a committee and is now published, and it's also published on the web, www.asha.org, American Speech-Language-Hearing Association, and is available for anybody who wants to take a look at it, so just one additional tool at our disposal.

I'm going to ask Sue Swedo to do a very quick intro on NDAR.

Dr. Swedo: So you've been hearing about NDAR for a couple of years, and I just want to introduce you to John White, who's sitting there on the side. John is the Project Manager for NDAR, and we're going to hear this morning from Matt

McAuliffe, who is the NDAR Technical Manager. We thought it would be great to hear from the guy who's actually building the system. So, Matt?

Dr. McAuliffe: Good morning. So, again, my name is Matt McAuliffe, and I'm the Technical Leader, and I'm responsible, along with John, coordinating with John, in building NDAR, building the infrastructure of NDAR to access information, the databases of the different types of information that's going to be generated as part of the ACE grantees.

So a quick overview, I'm going to do a relatively quick overview, a brief demo. First an overview, and then a brief demo of our particular part of NDAR, which is the clinical assessments tool that we've been developing, but I also wanted to note there will be a full demo during the break during lunch in the break room that you can learn a little bit more in-depth about the clinical assessments tool.

Okay. Our mission, as I see it from my perspective, is to help accelerate autism research by creating a collaborative infrastructure, and

that infrastructure is the hardware and software that'll allow the researchers to combine their data in a good way and allow them to extract information, query the databases, and then to generate reports and papers and science, essentially.

Here's a very high-level functional diagram of NDAR. Here are the main areas of NDAR. We have clinical assessments that we've been working very strongly in and making some very good progress and that we'll demo today. The neuroimaging -- we have a number of tools that are part of research that's done here at NIH as well as image processing tools that are a part of BIRN, and I'll talk a little bit more about BIRN in just a moment. And then the genomics-genetics track of NDAR.

The other really important part here is this area down here, the data integration, and we've begun doing a lot of work in that, in ramping that up. And the importance there is that you're trying to be able to query and retrieve data from heterogeneous data sets and to put that information together in a logical way.

So when we were looking at this, we wanted to look at what was already done out there in the community, and our research had found the BIRN, which is the Biomedical Informatics Research Network, so we wanted to build upon all the good things that they've been doing within that Network. So they've already built structures for doing collaborative research. They have grid computing tools. I mentioned the image processing tools, and importantly right now for us is that they have a number of data migration tools. So the idea is that we want to take some of the really good tools that are part of BIRN and build on top of those. And, in fact, we've taken some of our tools and already have installed them back into the BIRN infrastructure.

And so this is the BIRN, just to give you an idea that they're doing lots of interesting and important things, and we're going to take the bits and pieces out of here and use them and actually extend them in a number of ways. In fact, we just had a conference with the people who are developing Xnet, which is a tool that will help us

migrate the data into NDAR or to actually have federated databases across the different sites.

So our timeline, as Sue had mentioned, is that we plan to do some focus testing at the end of January with some of the grantees and then to actually have our Version 1 of NDAR to be available at the beginning of April and then a follow-on NDAR Version 1.1 at the end of the fiscal year of 2007.

So we've been mostly focusing -- we've got the infrastructure there, but now we've been focusing on the assessments, the clinical assessments portion of NDAR. And we did an evaluation of a number of tools -- I think it was a total of 11 tools back in January of this year, actually. And the evaluation showed us that the OpenClinica tool from Akaza Research was going to be the best tool, and one of the things that impressed us that was also a very good tool, and it was also an open-source tool. So we've been actually working very closely with them. We just had a working group, a clinical assessments working group, meeting yesterday where representatives from Akaza came

down. They demo'd their Version 2.0, which we actually had a lot of input into. In addition, we're building, on top of OpenClinica, our own extensions to it, including things like scoring skip patterns as well as a number of other features.

So what does OpenClinica do? It has an instrument library or forms library and management. It has subject tracking, study management, and then finally querying and reporting.

This is a list of the forms that have now been developed and integrated into OpenClinica. It's actually relatively easy to generate these forms using an Excel spreadsheet, and then they're transformed from the Excel spreadsheet into the OpenClinica database. And right now we have a total of 40 forms, and we hit a lot of the more important ones -- the ADI-R, ADOS, Vineland -- and we'll continue to add these on an as-needed basis. But we will also work with the ACE Centers and helping them develop new forms.

The one thing that I wanted to also mention --

Sue had mentioned also -- is that we're working with the publishers right now to get the copyright issues worked through.

Okay. So let's go ahead and do a demo of OpenClinica. Okay. So this is the opening page, and at the top menu bar here are categorized the major functions within OpenClinica with some of our extensions to the application. So a kind of a simple use case scenario would be to go in and first develop a study. So I'm going to go into the business administration portion of this, and there's actually a number of studies that have already, just for test purposes and evaluation purposes, been added in. There's a number of users. Users have particular capabilities. If you're a PI, you have different capabilities than somebody who's just entering data in from forms. And we also have a lot of case report forms, or I'll just use forms. In this case, we have ADOS modules loaded in and the ADI-R.

So we can go up to here, so we can manage the users and give them certain properties. Again, certain users only have certain capabilities. We

can manage the subjects and studies. So here's a list of studies. We could just go click into here and actually create a new study. I'm going to use one that's already in here. Okay. So once the user or performance indicators, develops the study, generates a study, you then want to manage that study, and so he can add forms into that study. And right now there's five forms listed in here at the moment, and he can choose which forms are important to that study. So the first thing he'll do is go back to managing that study and define event definitions.

Now there's a whole lot of other functionality here, and I'm just kind of glossing over a lot of it. But I'm trying to cover some of the more important parts of it. So you can define an event. An event is when you actually have a subject come in for an evaluation, for example, and for that event you might have a number of forms that the subject will need to go through. So for a baseline study, you could go through, and you can see that the forms that they need to have processed during the baseline study are the four modules of the

ADOS form. So you can develop a number of events. We're actually working with Akaza. Akaza is also working with caBIG, and they've developed a calendar as part of caBIG, which then will get wrapped into the next version of OpenClinica as well as some of the additions that we're adding in scoring the skip patterns and a number of other features.

Okay. So now that you've generated a study, you've identified events and the forms with the events, you're going to have to identify the subjects that you want included in your particular study. So in this case, here's a list of subjects, and then you add those subjects into the particular study, and then you would schedule visits for them to come in.

So the next step after that would be to actually enter data into the forms. So, normally, though, you would probably enter this data into a paper form and then have the person or the user who is responsible for entering data would take that form and then enter that information into the form. So they would come to the "submit data," and

here's a particular patient. They've already gone through two of the events, and they probably have at least the two forms already in there. So let's go take a look at those quickly. So here are the forms, and I'm going to go to Module 1 of the ADOS form. And here's a summary of that. And, actually, I'm going to go down to the score summary, and we can take a look at that quickly.

So these numbers are automatically generated. These are not something that you can enter, and that's why they're grayed out here. So at the moment, let's just look at the communication tool. The scoring for this particular subject was at 3, and that puts it in between classic autism and the autistic spectrum. Okay. So let's actually go back one level here, and I'll go into the communication section of this form, and we can take a look at that. Okay. So here's the form, and here are the data areas that you would enter into the form. A number of them are drop-down areas, at least in this particular form. And these drop-downs equate to certain values that are listed over here on the right. So if you identified this person with a

zero for this particular question, which is regular use of utterances with two or more words that would get a specific score.

Dr. Landis: This looks like a really great system, and I am credibly impressed how far it's come. I'd be interested in two issues. One is how much training is -- I mean I'm noticing you whipping around this, here we go there, and then we do this -- how much training is going to be required? What are the plans for training people who would be using it? And I think as important as inputting the data are how it's going to be used as a research tool to search the data and get things out. So I think you've certainly convinced me that this is an extraordinary way to get data in, but if we could talk about those two things, it would be great. I'm sorry to interrupt.

Dr. Swedo: That's all right. Maybe I'll pull it back this way then. Thank you. That was just absolutely fabulous. As Story said, it's very impressive, and I can speak to the training issue. It's actually easy enough for me to use, so everybody's used me as the illiterate standard by

which they needed to appeal to somebody who usually depends on my children who are graduating from high school and are no longer home to help. There will be training available, and the training module is being developed right now actually for the database builders and the data entry. But we actually had brought in a research assistant, sat her down at a computer the first day, and had her start creating instruments, and she was able to do them quite easily. So they're doing a great job that way.

The second question about the data sort of utility and the ability to actually have a national database is the reason that this piece is so important, is that having standard data entry to begin with allows that data to be seamlessly combined, merged, and used across the system. So one of the things that Matt mentioned as he was going through his introduction was this issue of data migration and importation, and that's the other huge piece that the NDAR team is working on right now so that the CPEA-STAART data, data from the CADRE Centers and all the rest of the data

sets, everything that's been done in ISAAC over the last decade, can be incorporated, put into that same infrastructure, the same framework, and then it'll be able to be searched.

Mr. Shestack: For imaging or genotypic data or other --

Dr. Swedo: Yes. As Matt pointed out in his introduction, it's sort of a three-part system at the NIH. There's the clinical assessments or the clinical studies piece, the neuroimaging piece, which is very heavily built on the BIRN, so that is state-of-the art, and actually, Matt's team was one of them that developed a lot of that software and a lot of those programs, so they've been able to just modify those as needed for the autism community. And then the third piece is genomics, and the genetics development team is working with folks at the NI repository, other groups across the country who are already doing the genetics work. We asked them to hold a little bit on this until we know what kind of need there is in the ACEs for genetics, because we didn't want them, for example, to focus all of their time on

microradiant analysis if that wasn't going to be the first data set to come in.

Dr. Insel: We've got one question from over here. Go ahead.

Dr. Pazin: I'm heartened to see that a demonstration is in Mozilla, but a lot of scientists use different OSs, so I have to ask will this be compatible OSs and browsers? Is it being --

Dr. McAuliffe: Oh, yes. It's compatible with any of the browsers. I just happened to use Mozilla. It's fine --

Unidentified Speaker: And does it run on a MAC?

Dr. McAuliffe: Yes.

Unidentified Speaker: Does it work on Linux and Apple's?

Dr. McAuliffe: Yes. Whatever -- I mean if they have a Mozilla browser installed on Linux, it's going to --

Dr. Insel: -- But the bigger problem is the ontology, so when you get into the neuroimaging arena, what one person calls amygdala may not be

what the next person calls amygdala, so there are a whole series of issues that still need to be developed to get the cross-site, cross-investigator, cross-institution vocabulary to be identical, and that's something that's being worked on through BIRN as well as through this project.

Dr. McAuliffe: Yes.

Dr. Insel: Also, there will be a real demonstration of this in vivo at lunch, and that's where, Matt?

Dr. McAuliffe: That's just in the break room.

Dr. Insel: Okay. So that'll be set up, and anybody who wants to surf this can do it. Last comments? Jon?

Mr. Shestack: I seem to remember that a couple of years ago that the CDC had its own proposal out for a data management center and awarded it to someone in Michigan -- I don't remember where -- it is in Michigan State. And are those people also coordinating with the NDAR effort to make all that data available?

Dr. Lajonchere: They're using [Inaudible

comment].

Mr. Shestack: That's lovely, but the utility ultimately is to bring in all those CADRE data, all that data into this system?

Dr. Boyle: Well, we haven't started collecting data for CADRE yet, but, yes, I can check up on that. I don't really know if they are.

Mr. Shestack: That would be a good thing for this group to know.

Dr. Boyle: Yes.

Mr. Shestack: Because that was one of the objects of the design of NDAR was to enable to assume data from various agencies and maximize the economic utility of it so.

Dr. Insel: Absolutely. This also brings up the issue of other nongovernmental efforts that are underway, and there's been lots of discussion with the Simons Foundation, with the Autism Consortium in Boston, with other groups that are here in the room, Autism Speaks about how to integrate across the different platforms, so the hope is that we'll have one IT repository for all of these efforts that are going on through all of these different

pathways much the way we have now for pediatric cancer. And that's part of why we've done so well in that field is there's been this collaboration and integration of information, so --

Thanks very much, Matt. We're going to go on to two additional science presentations. The first one will be from Dr. Katherine Loveland who, again, this seems to be our data here, from people from Texas. Dr. Loveland is a licensed psychologist who was Director of the University of Texas Developmental Neuropsychology Clinic from 1985 to 2000. She's currently Professor of Psychology and Behavioral Sciences Pediatrics and Biomedical Sciences at The University of Texas Health Science Center at Houston, and her work is on the development of communication and social behavior in persons with autism. It's been funded by NIDCD, although Dr. Beaudet has had to leave for a little while, and much of her work has looked at joint attention and on narrative language in persons with autism. She's currently one of the CPEA-affiliated program projects funded by NICHD.

And welcome to Yvonne Maddox, who's here from NICHD, and she's focused on the neurobiology and neuropsychology of autism and their relationship to social-emotional behavior. Welcome, Dr. Loveland. We're looking forward to your remarks.

Dr. Katherine Loveland: Thank you very much. I'm here today to talk to you about something we don't often hear about, which is girls with autism. I am, as you heard, part of the CPEA Network. And in my relationship to the CPEA Network, I've also served as the Chair of the CPEA-STAART Data Sharing and Common Measures Subcommittee, and that has been a very eye-opening and interesting experience in which I've dealt with many of these issues that we just heard about that affect the building of the forthcoming NDAR database system.

I'm going to talk to you about some work that we've been doing as a cross-network study on girls with autism and which illustrates many of the challenges that we actually face in attempting to combine data across centers that were not originally designed to share a common protocol and

which have many things in common but also many differences.

Well, we originally decided to study girls with autism because, as you know, girls with autism are fewer than boys with autism, and they have not been well studied. There's a lot of interest in them, but it's been difficult to study them. If you look at the literature, there are very few studies that are actually studied on girls themselves. What usually happens is that girls are included in the study but in proportion to their prevalence in the population or the amount of girls in the population we think are there, and that means that they are usually in too small numbers for us to do gender-related analyses, and that's a limitation with many, many studies that include girls.

However, there is widespread suspicion, particularly among clinicians, that there may be something different about girls who have autism that they could be different in their intellectual disability level, with social skills, possibly in the way they present clinically.

So our CPEA-STAART Networks have been collecting a large amount of phenotypic data over 10 years, and as we have worked on making a database that collects as much as possible of these data, we saw a unique opportunity to study girls with autism.

Now what are some more of the reasons why we should look at girls? First of all, we do know that autism displays a sex ratio difference, and there have been many estimates of this, but we do know that there are many more boys than girls with autism. Some studies have suggested reasons why girls might present differently and could be identified later than boys in some cases. And if that's so, it could be a real problem, because those girls might miss out on getting appropriate services and interventions that they would otherwise receive. We do know that other studies have shown that other developmental disorders have sex ratio differences and that may have differences in the way boys and girls typically present. For example, in ADHD we know that boys particularly are represented in the combined

subtype of ADHD, whereas girls tend to be more represented than boys in the predominantly inattentive subtype. Now that's just one disorder, but we know there's a considerable overlap with autism and ADHD and some of the symptoms. So there are reasons to think that we might find some differences. And as I said, if there are phenotypic differences between boys and girls, it could affect how we treat girls, how we detect autism spectrum disorders in girls.

Now, one of the things that's been floating around out there in the literature is the extreme male brain theory, and I mention this, which has been proposed by Simon Baron-Cohen and his colleagues, to illustrate the idea that there could be biological reasons why boys and girls might be different. Baron-Cohen has argued that people with autism have what he describes as an extreme form of the male brain. He's speaking here primarily about cognitive aspects. He's argued that people with autism have greater systematizing skills than in empathizing with other people and that this could have to do with early hormonal

environment, perhaps in utero. So this is not a theory that has been confirmed. In fact, it's very difficult to confirm. However, it does suggest some intriguing hypotheses that some people with autism might be sex atypical; particularly, females with autism might be shifted in some ways toward the masculine end of presentation.

So what I want to emphasize is that there is a need to identify phenotypic characteristics that might differ between males and females with autism, that we need larger samples than have typically been included, and we need to look at relationships among factors that affect how they function and what we would see if we perhaps are child psychiatrists or a pediatrician or any other frontline caregiver or educator involved with autism.

The goal of our study has been to look at participant characteristics and common measures, and I'll speak in a moment about what I mean by common measures and compare them between males and females with autism in our data set and then also to identify hypotheses that might need further

investigation from a differently conducted kind of study.

Now it's important that I explain to you where our data are coming from. We have data sets that have been combined from centers that did not set out to have the same common protocol. We went in there and included as many females with autism as we could who had all or most of what we call the common measures in the CPEA-STAART system, and these include verbal IQ, nonverbal IQ, the Vineland Adaptive Behavior Scales -- which, as many of you know, is a measure of everyday type of skills, getting around in the world type of skills -- the autism diagnostic interview and the autism diagnostic observation schedule, which, of course, are rather the gold standard now for diagnostic classification for people with autism, plus age, diagnosis, and sex. There are other things that we have in the common measures such as ethnicity and so forth, but not everybody has them, and not everybody has these either as we'll see.

Now not surprisingly, our data set includes a larger number of males with autism than females.

Out of all the CPEAs and STAARTs, we could get about 300 females that had most or all of these measures. That's great from the standpoint that there are not many studies that include that many females, but it's actually low when you consider how many people are in the CPEAs and STAARTs. So what we have here is a cross-sectional database ranging from preschoolers through adults of all IQ levels, so it's very heterogeneous. I'm limiting the analysis I'm going to report today to people who are 18 years or younger.

Now, one of the problems with this data set is that people at different centers, researchers set up different inclusion/exclusion criteria, so this is not an epidemiological sample. We didn't go out and gather data from just everybody we could to be representative of the areas that were sampled. For example, in my center, because of the needs of our research studies, we had a stratified sample, so the relationships between age and IQ were the same across boys and girls and across ages and IQs, so that is in no way representative necessarily of the population, so everything's been evened out so

that we could make our comparisons.

So the point I want to make here is that our sample is very large, but we cannot state that it is necessarily representative of the autism population. That limits some of the conclusions we can make. So we can't draw strong conclusions from this sample along the lines of girls have more intellectual disability on average than boys. We can't make that kind of conclusion out of this, because the sample is not necessarily representative.

Also, as you will see, we are combining not only data across centers but data across different measures. Our common measures are really constructs. They're not specific measures like ADI or something. They are really constructs. So, for example, we have several versions of the ADI that have been used, and you saw that reflected, I think, on one of the slides from the NDAR, there are -- it is characteristic of psychological measures such as ADI or IQ measures that they are revised and updated and also that they have different forms for people at different levels or

ages. Therefore, when we put together IQ measures or other things from different versions of a test or different tests, we're not exactly certain that we're combining the same construct. We have to guess. So we did our best with this.

Another problem is that since these things provide slightly different measures and slightly different scores and things, DM-STAT has had to do an enormous amount of work creating algorithms in order to combine these data in ways that are not misleading. We don't want to combine data in ways that are going to distort what's there. If we did, we'd have garbage in, garbage out, and we certainly don't want that. This is just to show you briefly the variety of IQ measures that we have used in CPEA-STAART, and keep in mind that there are also multiple versions of some of these. So it's difficult to combine these. Some might have a nonverbal IQ and a verbal IQ; others may have five different scales which we have to combine in some other way in order to derive a verbal IQ and a nonverbal IQ. So this is a nontrivial problem, and no amount of data-basing

is going to solve it. It's a matter of understanding the measures.

These are all the centers that contributed data. You will notice that there are many more boys than girls, and you will notice that some centers have very, very few girls. It may depend on their recruitment pattern, the needs of the study, but it is a challenge to get girls. My special thanks goes to Cathy Lord, who contributed 123 girls that were not part of the CPEA-STAART, and that was just to help us get our numbers up and also the University of Washington site contributed 91 girls.

Here are our research questions. We wanted to know whether there were differences between males and females in the relationship of IQ and age to measures of everyday skills and measures of autistic symptoms. We want to look at IQ and age because we have reason to think these are extremely important characteristics about the development of the individual, and so the measures we are using, verbal and nonverbal IQ, chronological age, Vineland Adaptive Behavior

Scales, and I've listed there the subparts of that which we'll talk about briefly, and the autism diagnostic interview revised, and it has subparts listed there as well. I'm not going to talk about the ADOS today. We haven't analyzed those data yet but we will be.

All right, briefly, the characteristics of the males, of the females in the sample, so we, what we see here on the left, we have verbal IQ, and on the right, we have nonverbal IQ. And those box plots the red line in the middle is the mean.

So what you can see is that males on average have higher verbal and nonverbal IQs in this sample than girls do. The width of the box represents the number of people in that sample, and the outer lines represent the variability. So what we're seeing here is males on average have higher IQs, but both groups on average have IQs in the below-average to moderately impaired range in this group, and sex differences on nonverbal IQ seem to be about the same.

Here are the differences in age in this sample. And, again, we see that the males are a

little older than the females. The majority of our kids in this sample are less than 20 years old. We have truncated it today. There were some adults in this sample, but we've truncated them because there are so few present. The majority of people in this database are children 15 years or younger.

Now let's look at the Vineland Adaptive composite standards score. What that is an overall measure of adaptive behavior from a number of different domains. It's a standard score, so it's a score that has been normed against aged peers. So this is a measure with 100 as the mean of how kids are doing relative to typically developing peers. And what we see here is that the majority of the participants in both groups have adaptive delays, so they have a mean in the girls' case in the 50s and in the boys' case in the 60s.

Now let's take a look at relationship of IQ to age. This is on the left, verbal IQ, and on the right, nonverbal IQ, and I've got some tests down there to show you. You can't tell much from just the dots, but if you look carefully there, you'll see I have some lines, and the females are the red

line, and the males are the green line. And we have a somewhat consistent picture. The relationship between age and IQ is not very different between boys and girls in this sample; so, on average, boys have a higher IQ score than girls in this sample, which is why the line is higher. And, interestingly, higher IQs are overrepresented at older ages in both males and females. And the reason that's of interest is ordinarily, since this is a normed measure that we're looking at, at least across all these measures, it should be flat at all ages because of the way tests are constructed. But it's not. It's going up. Now, does that mean there's something about kids with autism? Not necessarily. It could be just a feature of this sample. It could be that the older people in our samples were selected for things like imaging studies where people tend to get a greater number of higher functioning individuals. We don't really know. I could probably go back, and with a fine-tooth comb, figure out the criteria for admission into the different studies that are in here and figure out

why they were overrepresented, but it's probably not a feature of the population.

So let's look at adaptive behavior, how kids function in their everyday environments related to intellectual level. So I'm going to start with the communication, which is a measure of not of just how high your language is but how you use your language in everyday situations. And we're seeing a similar picture here on both sides, that is, with the verbal IQ and the nonverbal IQ, and the boys and girls look pretty similar, too. Both males and females with higher IQs have higher adaptive communication scores than do the ones with lower IQs, which is exactly what you would expect. That means individuals with greater intellectual level are doing better on adaptive skills. We would expect that. However, there's a significant interaction which shows us that this relationship is stronger for females than it is for males. Here are daily living skills, which are things like tying your shows and going to the bathroom and so forth, and we see a very similar kind of picture. Again, differences between the

sexes are a little weaker here. And socialization, again, we see a very similar kind of picture. Both are higher in those with higher IQ, but the relationship is stronger for the females. Now I don't know why that is, but there it is. And here again is the composite related to verbal and nonverbal IQ, and this simply combines the scores from the previous three that I showed you. So overall, adaptive composite scores are higher in people who have higher IQ, which is exactly what we'd expect in typically developing or people without autism.

Now let's look at adaptive behavior with age. Now this is rather different. This is the overall adaptive score that I showed you, except this is against age, not IQ, and it's flat, which means the older you get, it's not giving you necessarily an advantage. And that's especially odd, because we know that those older kids' high IQ is overrepresented in those older kids. So why is this not going up with age? That's interesting, but there doesn't appear to be a relationship of Vineland composite to age, and there are no

differences by sex. But this is interesting when you compare IQ to age versus adaptive behavior with age. So we know that IQ is positively associated with age, but Vineland composite is not. Thus, that suggests that possibly older and brighter individuals with autism are not necessarily showing an advantage in adaptive skills over younger and less able individuals as we would ordinarily expect, and that's rather interesting. So that's something that deserves further investigation. It may have, you know, implications for the developmental pathway of these kids.

Vineland communication standard score goes up a little bit over age, but daily living does not, so it's unrelated to age. But look at socialization. It's actually lower in greater age. Now I want to point out that because this is a standard score, it doesn't mean that older kids with autism are losing skills or that they have less social skill than younger ones. Remember that this is a score that is normed by comparison to age peers. So what it means is they're slowing

down; they're not keeping up as much with age. And that's very interesting. It relates to some findings that our group had in the late eighties and nineties on adaptive skills in adolescents with autism that suggest that, in fact, they were plateauing in their adaptive skills somewhere in adolescence and not keeping up, possibly because of the nature of the adaptive skills that we expect typically of individuals who are adolescents.

Let's look briefly now at the autism diagnostic interview and IQ. As you know, this is one of the chief measures that we would have in the common measures, because it is part of the gold standard for diagnostic classification. It has a number of subareas which are related to the *DSM* criteria. The social area in relation to IQ -- we see that the social subscale scores tend to be lower, and that is better. Okay? You want a lower score in those as opposed to the Vineland, where you want a higher score. So people who have higher IQ tend to have better functioning, which is to say less autistic symptomatology on the ADI

social. And that's not too surprising, and it seems to be similar in the males and the females.

In the communication area, we see that communication scores are better in the males with higher IQ, but this is not true of the females, and that's rather interesting. If you look at the score line for the females, it's much flatter on the right than the males, and I think this nonverbal IQ has something to do with that. So we have to unpack this a little bit more to understand why that might be.

Okay. Here's the repetitive scale, the repetitive and stereotype behaviors. Repetitive behavior scores tend to be higher, which is to say worse, in females but not males who have higher IQ. And I don't know why that is. That seems counterintuitive, doesn't it? So we're going to look further into that as well. We didn't find any relationships of ADI with age. And I want to point out that where we looked at verbal IQ, we also tried it with verbal IQ and age in the mode. And where we put age in, actually, the relationships with IQ got stronger. So this is a very complex

data set, and I'm giving you the quick run through on this, but it's a very interesting pattern.

So there are a number of similarities between males and females with autism so far that we've discovered. Adaptive skills are greater in both males and females with higher IQ, but individuals with autism might have lower adaptive performance than we'd ordinarily expect for their IQ. But because age and IQ are related in this sample, we're going to have to study this further, and we will have to unpack it a little bit more. Clearly, what we really need is a study that looks at this longitudinally. Right now, we've got a cross-sectional study, and you can never be certain about these developmental trends cross-sectionally. These data do provide evidence consistent with earlier studies showing the individuals with autism may plateau in the acquisition of certain adaptive skills, particularly in the social domain, as they get older. And the relationship of adaptive skills to age is similar in males and females in this sample.

We did find a couple of differences between males and females that are suggested by this data. Adaptive behavior is more strongly, which is to say positively, related to IQ in females than in males in this sample, so having a higher IQ seems to give you more of an advantage if you're a female than it would if you're a male. I don't know why that is, but that deserves investigation. And higher IQ is associated with lower autism symptom scores on the ADI for males but not for females in this sample.

Though these are interesting findings, we aren't, at this point, able to tell you exactly what they mean. However, I think that they do suggest hypotheses that should be followed up in other larger and prospective studies rather than the way we're doing it at this point, although this is a good place to start. So these preliminary findings do suggest that there might be phenotypic differences between young males and females with autism, and we should have additional studies to determine whether or not these findings actually hold up in a more population-based study.

I want to emphasize that I really think that there probably are differences in presentation. We know that females with autism are fewer than males. However, we don't know how much fewer. Probably every clinician in this room has seen girls with autism who are identified later than is typical. And, in fact, I saw an 11-year-old girl last year who I identified as having PDD because she had strong signs of an autistic spectrum disorder, but it had been buried beneath some other things that she had, and she was not strong in repetitive behaviors and things like this, and she was not a problem at school, so she had not been identified as having an autism spectrum disorders earlier in her life. One wonders how many girls there are out there who need to be identified as being on the autism spectrum who have not been.

I want to thank DM-STAT, particularly Emily Quinn, for the enormous amount of work that they have put into making this database ready for use. It has required a tremendous amount of data cleaning as well as writing of algorithms and ways

of finding patterns that can be used as equivalents in these data; David M. Lane for his statistical help; Stacy Reddoch and Deborah Pearson for help at my center; all the contributing sites have contributed a great deal to this; and Cathy Lord for contribution of additional girls. Thank you.

Dr. Insel: Thank you, Dr. Loveland. We have just a couple of minutes for questions. Story?

Dr. Landis: So I think the data are interesting, although obviously confounded by the fact that it's cross-sectional. I mean, so for the difference in older versus younger and acquisition of adaptive skills, I would assume that the older kids probably didn't have the same benefit interventions that maybe the younger kids would have?

Dr. Loveland: Well, that's certainly possible. It depends, really, on who they are and where they came from, and they're not that old. But you're -- they're -- we're talking about, you know, 14- to 18-year-olds perhaps. I'm not sure exactly which grouping of them is driving that result, too. That

would be something to point out.

Dr. Landis: So that's just one question. The second question is: are there clear implications of findings that you would get from this for diagnosis or treatment? And then the third is a comment, which is an alternative way to think about the fact that there is difference in prevalence in girls versus boys other than the straightforward genetics, is that rather than having a super male brain, the girls have more socialization skills which compensate, so it kind of turns it around 180 degrees.

Dr. Loveland: Well, let me comment on that second one first. Certainly, one of the things we wanted to address by looking at adaptive behavior was the possibility that there are social behavioral differences between boys and girls, and that may be in fact the case. And we need to be looking at little girls, I think, around the time of diagnosis to figure out whether or not they're presenting differently. You know, one of the problems is that, as we've done in heart disease in the last few years, we've discovered that women

were not being identified because they presented differently, and people were losing their lives because their heart disease was not being identified. And although autism is not life threatening, it's certainly important, and we have to look at ways that we might explore early symptoms of autism in young girls who might be coming up for diagnostic classification. And it is certainly possible, and a lot of people thought this, that social behaviors are better in individuals who are girls, and perhaps maybe these girls are not being identified for that reason -- maybe they're a little affiliative or their behaviors are less disruptive in some areas, and, you know, so we might be identifying only the ones who are more severely affected.

Dr. Landis: So you would argue that there would be benefit for diagnosis, but there's no reason now to think it would have -- that there would be aspects of this that would be relevant for treatment?

Dr. Loveland: Well, at this point, I think the best we can do is generate some really good

hypotheses to be followed up on. I think the data we have are limited by the fact that we have, you know, this cross-sectional data set that was derived from a lot of different centers, so we don't have any treatment data in this. I don't know how any of these kids were treated. I don't know what sort of programs they may have been in. One of the things I'd really like to know is about behavioral and emotional disorders that may or may not have been present in these kids. There's a lot of things that could be different. We don't know whether medication treatment needs are different between boys and girls. You know, if indeed there are cognitive differences, there certainly could be behavioral-emotional differences as well.

Dr. Insel: Story, if I can respond to your second question? There's -- one of the other places where there's been a really striking difference, male-female difference in kids with autism, is in this recent story around paternal age. It happened to be covered on “CBS Evening News” this week, but it was published as a scientific paper in the “Archives of General

Psychiatry" in September, and I happened to bring this up because I spoke to one of the authors of that this past week. If you look at kids with a history of advanced paternal age -- advanced here is over age 40 -- there's a much higher odds ratio. So the odds ratio that was reported in the literature was about five for males. Actually, the odds ratio for females, small group, was about 18.

But according to what I heard on Wednesday of this week, when you go to a larger set, the odds ratio goes up to about 200 for girls compared to boys. So if one is interested in identifying a subgroup who may have some form of genomic instability, might have an X-linked disorder, this may be a really interesting cohort to focus only on girls initially and to do CGH or to do genetic studies in that group looking for potential etiologic lesions, genomic lesions, that could pull out a subset that may have a slightly different phenotype, which is what Dr. Loveland is picking up.

So I think there's an opportunity here that just hasn't been mined, because we haven't had a

large enough sample.

Dr. Loveland: The combination with some epidemiological and genetic data.

Dr. Insel: Right. There's the potential. Other comments before we go on.

Dr. Loveland: I see that there's a question in the back.

Dr. Lajonchere: Two quick comments. First of all --

Reporter: Use the microphone?

Dr. Lajonchere: -- do you have any SRS data available that focuses on specific --

Dr. Loveland: No. We don't have any social responsiveness scale data. Some of the centers probably have used that, others have not. And, you know [Inaudible comment] --

Dr. Loveland: It's one of the measures that may be in the database, but since it was not one of the common measures, I don't have it here. There are a lot of things that would be really interesting to look at in the girls. The question getting enough girls and boys together who have the measures, and it was remarkably hard to get

this number of girls to have this much in common.

Dr. Lajonchere: Well, I heard -- I just wanted to kind of offer the agreement case, because we have over 1,400 families [Inaudible comment]

Dr. Loveland: Wonderful.

Dr. Insel: Thanks, Clara. Last comment. Then we need to go on, because we're falling behind again. Lucille?

Dr. Zeph: Question -- did you find any difference in the age of diagnosis?

Dr. Loveland: Well, at this time, we haven't looked at age of diagnosis. We may have that. Many centers do not record that or have not contributed that to the database.

Dr. Insel: Okay. Thank you very much, and we'll move on to the next presentation, which is from Dr. David Amaral from UC Davis. Dr. Amaral has, I think, been here for previous presentations, so he may be well known to most of us. He's the Foundation Chair and Research Director of the MIND Institute dedicated to understanding the biological bases of autism and other neurodevelopmental disorders. His research

includes both studies in nonhuman primates as well as in neuroanatomic studies using the human brain. And we're going to hear what is actually a historic contribution, I believe the first quantitative neuroanatomic study in autism that was published this summer. Welcome, David.

Dr. David Amaral: Thanks, Tom. It's a pleasure to be here this morning and to talk a little bit about some of the findings from our research over the last few years. I'm going to talk about stereology and the recent findings, but I want to set it up with some context of a previous study that we've done. And the more general context is that one strategy of trying to understand the etiology of autism is try and figure out which parts of the brain are most impacted, not only which parts of the brain, but at which time during the developmental time course they are most impacted.

Now as you all know if you look at a brain with autism, there's no obvious neuropathological defect, there's no atrophy, there's no frank lesions, yet a number of studies using both

imaging and now more and more histological studies have now shown that there are neuroanatomical problems in the brain. We have taken the strategy of looking at one particular part of the brain called the amygdala that has been implicated, for a variety of reasons, in autism. So for those of you who may not be familiar with where the amygdala is, this is a cross-section of the human brain, the corpus callosum here, the front, the back. The amygdala is this red almond-shaped structure here. It lies just in front of the hippocampal formation shown in blue. In the human brain, it's about a centimeter and a half in longest dimension, and of course it's bilaterally symmetrical.

And over the years, the amygdala has been implicated in a number of functions. Most notably, for those interested in its involvement in autism, is that it's been implicated in various aspects of socioemotional behavior -- probably most known for its role in detecting danger signals in the environment and generating a fear response -- but it's also been associated with memory modulation

and reward association. It has, in the past, been implicated in autism.

Probably the first sense that the amygdala might be involved in autism came from this very first neuropathological study by Margaret Bauman and Tom Kemper. They did a sort of standard neuropathological where they cut sections through the amygdala and then compared those sections with equivalent sections from a control brain but did it in a qualitative way using the neuropathological sense. And what they found was or what they observed was that in certain parts of the amygdala -- and the amygdala is actually a fairly complex structure, it has 13 different subdivisions, but it in these three divisions, the central, medial and cortical nuclei -- they found that there were clusters of smallish neurons that were tightly packed. And they suggested that that indicated that there was an arrested development of the amygdala, that these neurons hadn't generated all the connections and dendrites and whatever that would be typical of a more mature neuron.

Since this study, there have been hundreds of thousands of papers done on the amygdala, many of them using functional MRI in humans. And many of those papers have implicated continuously the amygdala in social and emotional development. And in a paper published in 2000, again by the prolific Simon Baron-Cohen, he assimilated all these data together and basically came up with what he called the amygdala theory of autism. And the basic premise there was if the amygdala is really important for mediating normal social behavior -- and one of the cardinal hallmarks of autism is a dysfunction of social behavior -- and if, based on the work by Bauman and Kemper, there is some pathology of the amygdala, perhaps this is at the heart of the autistic symptomatology.

And our laboratory, for years, has been interested in the amygdala, so we decided to study this hypothesis that, really, the amygdala was central. And we do it both in our human studies and our animal studies. And I'm just going to give you a little glimpse of what we found thus far in our human studies. Rather than go initially to

post mortem studies, though, what we did initially was to carry out an MRI study of kids between the ages of 7 and 18 to look at their amygdala to see if we could detect anything using structural MRI that was pathological in the amygdala.

Now, you'd say that certainly must have been done when you started thinking about this. And, in fact, in 2001 when we contemplated this study, there were five studies on the amygdala in autism. Two of them said the amygdala was bigger; two of them said the amygdala was smaller; and one of them said there was no difference. So we thought that that wasn't probably, you know, very conclusive. So we went ahead and redid it. And there's a lot of reasons why we think that those studies came to divergent opinions. But in part, it was that the, again, participants were heterogeneous, they were small numbers, and in a study that was published in 2004 by Cindy Schumann, who was a graduate student in the laboratory at the time, we tried to carry out a more comprehensive study.

One of the things we did -- and again, we

tried to have it as homogeneous a subject population as possible -- we used male subjects in this age range. We had four diagnostic categories -- low and high functioning autism, Asperger's, and normal controls. And we tried to exclude any kids from this study that might give confounding results, so we actually did have exclusionary criteria of seizure disorders, fragile X, and I should say that some of these subjects were actually scanned in collaboration with Allan Reiss and Stanford University.

We developed a fairly sophisticated algorithm to manually trace the amygdala, and this is just one of the brains of one of our subjects. And what you can see is in red here is the way we trace the amygdala, and we do this while we're viewing the brain in three dimensions so that we can actually get a very accurate rendition of the amygdala. And then, finally, what you end up with for your data are two-dimensional profiles of the amygdala from the front end to the back end. The computer sums that all up, and you get a volume.

So the first thing that we found that was of

interest to us, when we looked just at the normal kids, the typically developing kids from this age range between 8 and 18 -- and again, this is the left amygdala, right amygdala, but it shows the very same thing -- is that between this age range of 8 and 18, the amygdala actually plumps up by about 40 percent, so there's a tremendous growth in the volume of the amygdala over this age range, which is actually interesting because the total brain is decreasing in size by about 10 percent. So this is a disproportionate growth of this one part of the brain during the preadolescent and adolescent phase of life. We don't know what accounts for this, and actually we're now in the process of doing some nonhuman primate studies to try and figure that out.

But then if you look at the kids with autism and superimpose them on this graph, what you see is -- these are the three diagnostic groups, so this light blue, for example, is the high-functioning; purple here, low-functioning; and Asperger's, that during this age range -- there's actually a plateau of the growth of the amygdala.

In fact, what it looks like is that the amygdala has achieved an adult size by the earliest time that we were looking at these kids.

In looking at it a different way, if we break that group from 7 to 18 up into two subgroups, now this is 7-1/2 to 12-1/2, and I'll show you the older group in a second, and now these are all the kids, the MRI volumes of all the kids that are in the low-functioning, high-functioning, Asperger's, and control. What you see is that on both sides, the amygdala is significantly larger in the kids with autism compared to the controls. But if you look at the older kids, there's no difference.

So what's happening, we think, is that if you look at the development of the amygdala in the typically developing kids, they go through this protracted preadolescent and adolescent growth phase where the amygdala grows by about 40 percent in volume. The kids with autism, however, start at adult values, and they don't change over that period of time so that there's been precocious growth of the volume of the amygdala. And we've seen adult size of the amygdala at 7.

You could imagine then -- that's 40 percent -- that depending on when you look at the amygdala and compare autistic groups with control groups, you're going to get very different findings. So as it turns out, these are real data from the literature, that our study and actually a study done previously to ours by Sparks et al. at the University of Washington show that if you look at young kids that the amygdala is larger as we showed in the autistic kids than in control kids. If you look at adolescent or even -- adolescent kids -- there may be no difference. And then if you look at older individuals, the amygdala actually may be smaller. So it all depends on when you look at it what answer you get.

So the next question that we asked was what might account for the abnormal growth pattern in the amygdala in autism? And here I can't tell you an answer. I'm just going to tell you one of our approaches. The fact that the amygdala is larger could result from the fact that there perhaps were more neurons generated, more connections generated, or it may have nothing to do with

neurons or synapses. It may actually be due to increased glial cells, perhaps secondary to inflammation. It could be more vasculature, or the cells could be larger. All of these are possible, and we certainly haven't investigated all of these at this point in time.

But one of the things that we were interested in finding out is whether these changes could be accounted for by something to do with the number of neurons in the amygdala. Are there more neurons in the amygdala? A relatively straightforward question. The way we approached it then was to carry out a post mortem histological analysis of the number of neurons, and this goes back to the kind of study that Bauman and Kemper had done in the 80's.

The way we did it, however, was using a slightly more modern and quantitative technology. But again, just to go through how this gets done, first of all you obviously have to obtain appropriate brains from individuals with autism and control brains. You block the brains. And we used this technique that's called stereology, and

I don't want to go into a lot of detail about why we selected this, but the bottom line is all the previous studies in the past have analyzed brains and come up with a density measurement, number of neurons per unit volume. And the problem with that is that tissue shrinks variably during fixation. Depending on how you process the brain, you could get variable shrinkage. And so, of course, if you get variable shrinkage and it's undetermined, you could get a spurious difference in the density of neurons.

The only way, as it turns out, to interpret pathological changes in the number of neurons is actually to count them, and stereology is a method that was developed about 25 years ago for counting neurons that's completely independent of volume changes during tissue processing. Alright, and it gets used for all kinds of studies, but it's actually now the required form of analyzing neuron numbers in the brain. You can't publish a journal article any longer about neuron numbers unless you use these stereological techniques.

We again acquired brains. One of the rules

about doing this kind of study is that you actually have to sample sections throughout the entire brain region. So you can't take a little piece of the amygdala and sort of sample and get an answer. You have to take systematically sections throughout the entire amygdala, so one of the problems is that we had to obtain brains that still had the amygdala intact so that we could cut sections throughout it. You then take the block that contains the structure of interest, you cut histological sections, and you start analyzing them. And the beauty of this technique -- it's tedious -- but the beauty is that there's rules about how you analyze whether a neuron is there or not.

And again, you use a computer system. The computer generates a strategy for you where what you simply have to do is sit at a microscope, focus down through the section, identify that a neuron's a neuron. If it's in the safe zone, which is outlined by this area and the green lines, you count it. If it's not in the safe zone, you don't count it and you go on. And you don't have to

count all the neurons in the amygdala, but you actually have to count a representative sample of them, which still takes a fair amount of time.

You can also use a similar technique called the nucleator, and you can actually measure the size, the cross-sectional area of the neurons. So we did this. And not only did we do it in the entire amygdala, but we actually identified subnuclei, which I have color-coded here, of the amygdala. And again, each one of these we know a fair amount of in terms of its connectivity and some of its functional attributes based on our primate studies.

Where did we get our brains? Well, this was really a collaboration. Most of the samples that we were able to retrieve came through the Autism Tissue Program. Owe a great debt of gratitude to Jane Pickett, who helped us with the early stages of this project. So we've received tissue from the Autism Tissue Program, from the NICHD banks, as well as from the Harvard brain bank. One of the critical things about this study is that Margaret Bauman's studies in the past, and as far as I

know, every other study on autism, have used brains from individuals that had comorbid features, and the most significant comorbid feature is epilepsy. So in the Bauman and Kemper studies, for example, about two-thirds of the brains had comorbid seizure disorders. So the problem with that is that we now know from work that's been done on people with seizure disorders, you get pathology in the amygdala, and you get pathology in the hippocampus, and you get pathology in the neocortex, so how can you determine what is autism dependent and what is seizure dependent or some kind of combination of the both?

So in our case, we selected brains from individuals who did not have comorbid epilepsy. And the other thing that we did was that we age-matched them. So there were nine samples, you can see, going from 10 to 44 in our autism group, 10 samples in the control group that went from 11 to 44. So as far as we could, we tried to match these samples for this study.

So what did we find? Well, first of all, by

doing these stereological measures, you can actually get another index of the total size of the amygdala. And now, remember, these are from relatively mature individuals, 11 to 44 and what we found was there was no difference in the volume, that the volume of these adult amygdalas, as our MRI studies had suggested, weren't any different. We also found that there was no difference in neuron cross-sectional areas. And here's one difference with the Bauman and Kemper study. They said that they saw these little tiny neurons in clusters. We actually didn't see any evidence of this when we looked at it quantitatively. So even in the central nuclei and in these remaining nuclei, which would be in the areas where Bauman and Kemper have said they saw small neurons, we didn't see any evidence of it in this group of brains.

Where we did see a difference, which actually surprised us initially, is in this finding. There's actually a reduced number of neurons in the autistic amygdala. So if you look, for example, here in the largest nucleus of the

amygdala called the lateral nucleus, in the controls, there's about 4 million neurons, whereas in the brains from the autistic individuals, there's about 3.5 million neurons.

If you look at the total amygdala, whereas most typical brains have on average about 13 million neurons in the total amygdala, in the brains from the individuals with autism, there were about 10.5 million neurons, so that's a significant and substantial loss of neurons in the amygdala of these mature brains.

So to conclude then, there's a lot of pathology in the amygdala. It doesn't necessarily hang together at the moment that one leads to the other. So from our MRI studies, we found that the amygdala volume is larger in young children but not adolescents with autism. In the typically developing kids, we showed, as I mentioned, that the amygdala volume increases by about 40 percent between the ages of 7 to 19, but since the kids with autism, their amygdala was already at adult size, you don't see that preadolescent and adolescent growth in the autistic amygdala. And,

finally, from the stereological studies, which as Tom said, is really the first quantitative study in autism, there's actually a reduced number of neurons in the amygdala both in the lateral nucleus and in the total amygdala.

So, at the moment, we can't explain these reductions in neurons in the amygdala. We hypothesized in the paper, and this paper was published against Schumann, this first author, this past summer, that there may be an ongoing process taking place here, whereas the amygdala may be hyperactive early on in developmental life. That hyperactivity may actually be detrimental to the amygdala over the long range. Because what we know, one of the things that the amygdala does when it's hyperactive, is that it drives the HPA access, so you have potentially dysregulated cortisol levels in the system. Those deregulated cortisol levels, Bruce McCune has shown, are able to feed back on the amygdala and actually to cause neuronal damage. So it may be that there's a long-term process. Again, we don't understand much about the mechanisms, but it's clear that the

amygdala is pathological.

And I guess the last comment I'd make is this support for Baron-Cohen's hypothesis that the amygdala is sort of an important aspect of the etiology of autism. We actually think not. And this, again, I think, is not definitive, but in our monkey studies where we eliminate the amygdala bilaterally, if we would expect a major dysfunction of social behavior, we'd expect there to be perturbations in the abilities of these animals without an amygdala to perform socially. But what we find is, actually, they're more social, that monkeys without amygdala are actually hypersocial. They're not hyposocial.

So our take on the whole story is that the amygdala, as I said early on, first and foremost is acting as a danger detector. It's there in our brains for detecting threats and for generating a response to threat. If the amygdala, as I think it is, is abnormal in autism, my prediction, at the moment, is not that it's dysregulating, first and foremost, the social behavior of the individuals, but it's dysregulating their fear behavior. And as

you all know, an important comorbid aspect of autism is dysregulated fear behavior.

A lot of hypotheses -- a lot more work to do. And I have to say that this, the initial funding of stereological studies, was when the National Alliance for Autism Research was actually the National Alliance for Autism Research, and they had faith in us and supported us as well as the work has been supported by the National Institute of Mental Health. And I have to say that it also has been supported by the families who come to the MIND Institute to get their MRIs. So thanks very much.

Dr. Insel: Thank you, David.

[Applause]

Dr. Insel: We've got 5 minutes for questions or comments. Sue?

Dr. Swedo: David that was beautiful data. Thank you so much. I'm just curious. If the neuron number is down but the volume is the same, what's in that space, or is it just space?

Dr. Amaral: Yes. It's -- you know, the way you do these studies is that you look at one thing at

a time. We've looked at neuron number. There are obviously lots of things that can be filling in the extra space. One of the things we're actually currently looking at now is microglia. You know, there's been a sense that maybe in certain cases of autism, there could be inflammation. Inflammation could actually be damaging to the neurons and replacing them with, you know glial processes. We haven't completed those studies, but we're in the midst of that. So the short answer is I don't know what's in that extra space. It's simply just not neurons.

Dr. Insel: Other? Yes, go ahead.

Dr. Landis: As it comes to me, I was going to say not neuron cell bodies. There could be extensive neuropil, which wouldn't necessarily be Nissl positive but --

Dr. Amaral: Correct. I should say, too, that the more fundamental question of, as the amygdala is growing in that preadolescent and adolescent phase in typically developing kids, we don't know what's leading to increased volume. And, fortunately, we're actually just starting now a

longitudinal study in the monkey to do both MRIs and histological analyses. It turns out in the rhesus monkey, you see the same protracted growth of the amygdala, and we're going to be able to do things like Golgi studies and other kinds of studies to sort of figure out what's going on in terms of the normal development. Again, it still doesn't answer what's going on in autism.

Dr. Insel: Katherine?

Dr. Loveland: Yes. Thank you for a very fascinating topic. I --

Dr. Insel: Please come up to the microphone up here on the side or you can use the table.

Dr. Loveland: Thank you for a very interesting talk. I was going to ask about your explanation of the role of the amygdala in autism. If you have damage to the amygdala, developmentally, and you're poor at detecting things that are threatening versus things that are not threatening, would that not impair your social behavior?

Dr. Amaral: Well, it's a good question, so we've answered that in the monkey. So we've done

lesions in adult monkeys, and we see that they can actually perform socially as control monkeys or animals with a hippocampal lesion. So there's no impairment in adult animals. But that question keeps coming up. Well, but you need your amygdala early on to learn social behavior. So we actually carried out a series of studies that's ongoing where we made bilateral amygdala lesions at 2 weeks of age at a time when rhesus monkeys are actually not interacting very much. Those animals now are 3-1/2 years of age, and while we do see differences, mainly in the realm of fear behaviors, they are completely socially competent.

So they probably do have dysregulation of their fear system, and we've seen actually pyridoxal situations where these animals are both more social, that is, they're making more approaches to other animals, they're interacting more, but they're actually more fearful while they're making those approaches. So it's somewhat complicated.

But just not being able to detect a threat or being able to do that appropriately doesn't seem

to abolish the ability to socially interact. If you're more fearful, it in fact may, as in what we think might be going on in autism, we would suspect that the kids are actually more fearful, that they're actually better at detecting threats or that things that are typically benign are now threatening. If you have an enhanced fear system on top of a social deficit, it's sort of a double whammy. So then that, you know, could lead to an exacerbation of your core symptom of autism. But we don't think that the amygdala lesion is actually leading to the core deficit in autism.

Mr. Grossman: Well, it strikes me that it's always been puzzling with individuals with autism -- there seems to be a lot of heterogeneity where some individuals are very avoidant with social stimuli and others are rather, you know, indifferent. So there really could be heterogeneity with respect to how the amygdala and the fear system is involved.

Dr. Amaral: I agree, absolutely.

Dr. Insel: I think David would be the first to say that volume isn't the only thing you could say

about the amygdala, so how it's connected is probably a lot more about how it functions, and there's a whole other set of studies which we'll have him come back to talk to us about that have to do with --

Dr. Amaral: -- Right, 5 years --

Dr. Insel: -- how the amygdala functions within the rest of the brain. We're going to have to break at this point. We're right at the end of this morning's session. Thanks to both of you for these excellent presentations. The NDAR demonstration will begin next door. We'll reconvene after lunch at 1:30. Let's actually try to get back a little bit before that so we can start right on time. Lee? There's a Services Subcommittee meeting now for those -- get your lunch --

Mr. Grossman: The Services Subcommittee is in Room 4A52, Fourth Floor, A Wing, Room 52.

(Whereupon, a lunch recess was taken from 12:12 p.m. until 1:28 p.m.)

Dr. Insel: We have a lot to accomplish in this next hour and a few minutes. Wait just a moment

here while people find their seats. The afternoon will be divided up into this next session, which is an evaluation of the IACC Autism Research Matrix, and the second half after the break will be a focus on environmental aspects of autism. I'm going to kick off this evaluation discussion, and then David Amaral and Denise Resnik will do the bulk of the presentation about the evaluation.

This should look somewhat familiar to you. This is the original Autism Matrix from 2003 that was voted upon by the IACC at that point in November of 2003. At the meeting that we had in May of this year, the Committee felt that it was time to do an evaluation of where we are 3 years into this. We brought a group together on the 25th of September to hold a full-day meeting to look at the different pieces of the matrix and to figure out where we had made progress, where we needed a midcourse correction -- not quite midcourse but 3 years into a 10-year plan. We had 22 people at that meeting, including public members, and did this by assigning individuals to take on specific themes. We broke this into eight themes so that we

could get through this very extensive, and as you can see, rather complicated group of, I think, 30-some items that were laid out over a 10-year plan.

The final part of that daylong meeting was a discussion of the gap areas and opportunities for future research. This is the group that came together, and many of the people are people that the IACC has heard from at various times in the past. An asterisk are those who were actually on the original -- I'm sorry, that's a different group -- but many of the people who are on here were people who were on the original autism matrix committee. And then those who have the asterisk were part of a second meeting that was held as a conference call on the role of the environment which people who didn't actually attend the meeting on the 25th but were involved with looking at some of the recommendations.

So what we want to do today is we'll hear from David, who I hope is here, to take us through some of the major findings. You have a draft copy of that. Those were distributed. There are many more copies on the table by the door. Denise Resnik

will then take us through kind of what next, and just to sort of preface her remarks, let me just say something about what we should expect to come out of the next hour, because we are not going to be facing a vote today on the document. What we really want is to put this out there in its current form to get comments from the IACC and from a broader community as well. We'll have a site on the website where people can send in comments over the next 2 to 3 weeks so that we can get additional thoughts about how to do this.

The most important piece of what we want to hear from you today about is not only changes to the evaluation as it's being done currently but also where we take it from here, what the action plans ought to be, and Denise will speak a little bit to that. But the plan that we have so far would be to put together about three workgroups -- probably based on areas like etiology and pathogenesis for one, diagnosis and detection for another, interventions for another -- that will take these recommendations and turn them into real plans, setting priorities, figuring out who will

be responsible for implementing these goals and who will be accountable for their completion, and we'll have some time to talk about that after Denise's presentation as well. I just really want to set up what we should be expecting coming out of today.

And then I think the ultimate plan will be to bring this back to you in May -- at that point, have much more of a fine-grained plan with a lot of elements to it. And, ultimately, we really want to see this is as a kind of living document, not as something that we visit every 3 years, but something that gets continually renewed and becomes a basis for setting priorities and for moving forward. So that's the setup. That's what we'd like to accomplish in the next hour.

David, if you will, if you want to take us through your overview of the discussion that was held on the 25th, we'll have your slides up here.

Dr. Amaral: I think that I've decided to keep my comments pretty general, and I will probably skip through a couple of slides here. But I think the group that came back and evaluated the matrix

clearly see the matrix as a living document, something that has to evolve over time. It's sort of like a research protocol that you try some pilot experiments and you come back and you alter it, get it to the point where it's really doing what you want to do. But I do think that at least at that slice in time in 2003 and the comments that have come up recently reflect a consensus that there's no single correct approach in determining the causes of autism.

We're not at a point, and this is not going to come as a surprise to anybody, but we're not at a point in time where there's one magic direction. We have to be pursuing a multiple directions. Several pathways will have to be pursued, and I think one of the things that I was impressed when I was in the process of the matrix is that it really is true that bits of pieces of the matrix are being carried out by this loose confederation of both public and private initiatives. And to whatever extent those and I know Denise will be dealing with, public and private initiatives can be integrated, that will be a really good thing

for the future of autism research.

And this is one of the things that probably didn't come out of the meeting, but it says "brainstorming about critical research should be an ongoing process with increased effort to integrate across levels." And I guess as I've aged, I've become more and more appreciative of the wisdom of committees and of information being shared, but I'm also impressed that it has to be done on a regular basis. So I'm glad to hear, for example, the idea of workgroups is something that will be discussed, because I really firmly believe that to have a meeting once every 3 years and discuss something like the matrix is not enough. It should be evaluated on an ongoing basis, perhaps every half year or every 3 months.

So this is taken from the document. It says "while progress is being made at the 3-year mark, the overall Autism Research Matrix represents at least a 10-year effort to best understand the disorder and identify the best treatments." So, really, this is early on the stage of trying to implement even the initial research matrix. And I

think the panel in general, everybody around the room or table that day, agreed that it really has been the last 3 years significant progress and capacity building, and that there's opportunities and resources available to autism researchers now that didn't exist 3 years ago. And so that's clear.

I think there's an infrastructure stage that had to be developed, and so to expect that there would be much more progress than has been made, I think, would be unreasonable. There's a lot of initial steps that have to be done, and those have been moved ahead.

The other thing, I think, that came from the discussions in the room is that while nobody disputes that genes are important in the ultimate etiology of autism, that environment is going to play a role as well. And in actual fact, I think there was quite a bit of discussion of the idea that it may well be that we're dealing with multiple types of autism that might have variable contributions of either genetic underpinnings, genetic and environmental underpinnings, and/or

simply environmental factors.

You know, I know that we're doing some work in our own lab on potential immune basis of autism, and sometimes people say well, you know, but this is an incredibly concordant disorder in monozygote twins, how could the immune system have anything to do with it? Well, as far as I know, the immune system actually is regulated by genes, and so even if it's -- there are immune factors -- they'll probably be a combination of both genetic and environment contributions.

These are the eight subject areas that Tom was mentioning, and here's where I'm going to start abridging my comments. It is -- there's a whole 2- or 3-day meeting revolved around the epidemiology of autism and how to take some of the matrix recommendations and run with them. Art Beaudet, for example, said, well, isn't there really some way to go retrospectively and figure out whether there's been an increase in prevalence, because if there is, you know, we could answer the important question that maybe some epigenetic factors like DNA methylation should be taken more seriously?

And, you know, he raised the question, and there was a little bit of conversation and then nothing. So I think, you know, this is a whole area that I haven't even covered that I think could stand days and days of conversation.

So I just wanted to go through a couple of these, and I will make some comments and then I'll conclude. One of them was characterization of autism spectrum disorders in associated genetics. One of the areas that it was agreed that there has been some progress is into defining an Autism Phenome Project. And we heard Sue Swedo talk about this morning. One of the comments that came up about this, though, was that there wasn't enough knowledge in the greater autism community about what was going on in terms of defining the autism phenotype, and I think it speaks to the issue of even increasing more communication within the autism community.

Things that haven't gotten very much underway -- animal models, determining susceptibility genes, and, of course, this is a long-term goal of finding both the genetic and nongenetic causes of

autism. We're really at the very beginnings of that. And, in fact, these kinds of things may depend on better definition of the autism phenome.

There was a consensus, I think, that we weren't talking enough about the environment, and as Tom said, there was a follow-up phone conversation with investigators that thought more about this. And one aspect of -- again, since the matrix is an evolving document, it's clear that any in new iteration of the document, there has to more attention paid to environmental factors. But again, in the very first iteration of the matrix, there were 13 people in the room not representing the totality. It was a good attempt at representing the totality of science, but people who are more involved in environmental aspects, you know, didn't have much of a say in that first matrix, and I think that that can be rectified.

Neurosciences -- this is the only other one that I will make some comments on. So there was a goal in the initial matrix to define the neurocircuitry and neurochemistry that's impaired in autism. So, for example, what's the

neurocircuitry that underlies social behavior or repetitive movements? And this is what NIH does spectacularly. There's lots of work going on in these areas. So there has been substantial progress on that.

But then other issues like trying to define the neuropathology of autism that I think has progressed relatively slowly. And part of the reason is that in order to do -- as I talked this morning about our stereological studies -- in order to make progress like that, you have to establish an effective process for acquiring high-quality post mortem brains. Just to give an example, so Francine Benes, who is the Director of the Harvard Brain Bank and oversees the autism repository at the moment, this is the state of the situation -- she has in her repository only 79 brains, and of those 79 brains, they're prepared in different ways, so some of them have been fixed for a long period of time and can't be used for something like immunohistochemistry. Only a few of them, 10 of them are fresh frozen so that these would be the ones that could be used for molecular

neuroscience, and some half and half. The bottom line is that compared to something like Alzheimer's disease where there's literally been tens of thousands of brains that have been looked at, we're still in the, you know, probably less than 100 that are available to researchers now. And this is a real impediment, I think, to future progress, but it could be solved.

So I'm going to skip all this. I think two areas that came out of the daylong session where we thought that new initiatives had to be implemented was one that I mentioned already -- analysis of environmental factors in the etiology of autism and then development to realistic animal models. At the moment, I think it's fair to say that there really isn't an animal model of autism.

An animal model of autism that's realistic, that's based on some of the known clinical features of autism could be enormously helpful in looking at the mechanisms underlying the pathology of autism as well as trying to develop interventions. But, in fact, there wasn't an element on the old matrix that said “develop

animal models." It was embedded within some of the genetic aspects.

And so my last comment is just, again, to, because I didn't know you were going to say it, task force development, but the idea of having an ongoing iterative process to refine the matrix, to provide integration and oversight of the research agenda, I think, would be enormously helpful to the field of autism. It'll speed it up. It's obviously okay to have redundancy built in, but the less redundancy -- or when you need redundancy, it should be built in. When you don't need redundancy, it's a waste of effort, and I'd like to see as little wasted effort as possible as I'm sure everybody else would. So I'm going to stop there and turn it over to Tom.

Dr. Insel: I think what we'll do is instead of taking discussion now, let's hear the next set of comments, and then we'll open this up for a fuller discussion from the whole group.

I'm delighted to have Denise Resnik here all the way from Phoenix. Denise is the Chair of the Southwest Autism Research and Resource Center and

has done a huge amount to build a program in Arizona, which is now really statewide, and for the whole Southwest. She was part of that September 25th meeting and had a lot of great ideas, and we thought that we would bring her back to talk about next steps and to help us think about where to go from here.

Ms. Denise Resnik: Thank you, Tom. The presentation that I'm about to share is a collaboration between Autism Speaks and the Autism Society of America, Cure Autism Now, and SARRC's logo looks like it didn't quite make it there, but let's see if we can pull it up. Nope, it didn't make it. And I wanted to thank Alison, Cathy Pratt, Sophia Colamarino for your participation and help in this presentation. Our organizations share a number of things in common. We share the sense of urgency. We represent families. We're committed to those families. We're committed to answers. We're committed to a better quality of life for our children with autism and their families. And so when we look at the research, we're looking for accountability, we're looking

for research that's actionable and truly going to improve the quality of life for us all.

So when we looked at advancing the matrix, we looked at the need to articulate some measurable goals. As we sat there in that meeting, we were forever, I think, perplexed at just exactly how should we measure the different initiatives, because there weren't specific goals that were identified; they're statements of different areas of research. And then we need to prioritize those goals, and prioritization of those goals also means resources and how we apply resources to the highest priorities. We need to define better outcome metrics. How are we going to evaluate the goals, and how are we going to evaluate the research and to determine what's next and improve accountability? Because, truly, we collectively are running a marathon here on autism. But we have to recognize that many times, it's a relay race, and what David Amaral does at MIND Institute and with the phenotype project needs to be handed off to another research group or another research collaboration, or he'll do it himself. But the

idea that we are working on this together and we need to have an integrated approach and one that's recognized through a matrix or another document.

We also need to explore best practices. When we talk about best practices, we're looking to other diseases and disorders, what have they done to advance their causes and then for all of us to promote evidence-based practices for autism, once again looking at how we can improve the quality of life for our children and their families.

So currently, you can see how the goals are articulated or how the matrix is identifying the goals -- individual, characteristics that predict response to behavioral, pharmacological, and other treatments identified. Well, that's a very difficult thing to measure in a group of 22 people or more or less. So what we were looking at is how can we look at specific metrics like identifying five or more characteristics that would predict response to behavioral, pharmacological, and other treatments? And we need to look at greater specificity in identifying these goals.

And, David, on the brain tissue, as an

example, recognizing that there are 79 brains. We know that this, and through the Autism Tissue Program and other work that's being done, it's a tall order, but we need to understand from you what 60 brains will get us, what do you need, you know, beyond saying that we need to collect more brains, so the greater specificity that you as researchers can have, the better off we as organizations and advocacy organizations, parenthood organizations can have in helping you to achieve maybe that phase one, then that phase two and phase three goal. I don't know about you, but when I'm exercising, and I punch in 45 minutes, and I'm exhausted at 40 minutes, I'll go 5 more minutes. If you could help us understand not just with brains but with other tissues, other samples, other things that you as researchers need, it would be most helpful to us as families.

And the matrix, as you saw, with all of its beautiful colors, does a very good job at identifying the different research silos, if you would -- neuroscience, epidemiology, genetics -- all very important to advance the cause. But what

we want to do is we want to look at the cross-disciplinary approach to our goals and to the research, because they need to be integrated, and we need to understand where that integration takes place at what points. Both David and Tom reflected on the need to look at these goals also in terms of detection and diagnosis, etiology and pathophysiology, and interventions.

So once again, as organizations representing families and as a great resource for all of you, what will have the greatest impact now and the greatest impact on the future? And truly we're looking perhaps at more than a matrix. What we need truly is a strategic plan, a strategic plan that's going to help us both with the short and long terms.

If you look at the matrix, I'd like to bring your attention to the y and the x axes, and during the review committee, I don't recall, and I don't think my colleagues do either, any discussion of the low-, medium-, and high-risk research areas. This is very valuable real estate on such a matrix. What we'd like to consider, if we do

choose to continue with the matrix format, is that we look at priority versus risk and then we look at the x axis on those areas that we identified earlier. I'm not sure yet what the colors mean, but I needed to fill in some space. But I think the colors should mean the integrated approach to the research and all the different disciplines that would be involved. So, truly, we will have a rainbow.

Right now what's constituting progress is the number of grants, the dollars that are awarded, the number of publications, but once again, we're looking for how is this going to impact individuals with autism and their families. What do we do today, tonight, the school year in terms of those effective treatment approaches and interventions? And how do we help build an infrastructure for more research, better research that is going to help give us answers and advance us toward the causes and the cures.

Throughout the process of evaluating the matrix, we looked around the room a number of times to determine, well, who's responsible, and

currently we don't really know who's responsible in terms of the clearly defined roles and responsibilities between the advocacy groups and the parent-led groups, our researchers, and the different institutions, and yet we're all trying to work together. So where the NIH starts and stops, where the advocacy groups start stop, and we need to look at this together and really proceed together.

So once again, I think we need an integrated approach of who's responsible yet somebody does need to be responsible, because what we do in terms of providing subjects and controls and samples that researchers need is obviously going to be a direct result of how far you get with the research. And we need to have stated consequences if you don't meet your goals, because we're depending on you. In any kind of integrated approach and any kind of teamwork, we need to be working together. We need to trust that progress will happen, and it will happen when we identify it will happen. And we know that things don't always go as planned, so along the way, we'll need

to allow for some course corrections, but we're not going to allow for excuses. We need to proceed. We are -- you know, we look at our watches. We live with our kids. Each and every day counts for us, and we need to move as fast as we possibly can. We also need to reward and acknowledge collaborations and value that teamwork and that integrated approach.

We've yet to identify where that roadmap is for diabetes -- but perhaps one exists -- or the research matrix for breast cancer, the strategic plan for AIDS, but we need to understand how advocacy groups have worked most effectively with the NIH to fight other diseases or disorders. We need to stand on the shoulders of others who have come before us to look, you know, the mistakes perhaps that they made, how they were able to make their greatest advancements, and we need to do better.

And when we think about interventions, we're looking at both the clinic and community based. We understand there's a lot of focus on the early-childhood and early intervention, but we also

recognize our kids are growing up. This is actually a picture of my son Matthew at a restaurant -- this was one of our vocational programs at SARRC -- wearing his earphones because of the heightened sensitivity that he has to the noises. We need to better understand both in the clinic and the community-based settings what's going to be best in terms of interventions for adolescents and adults. And we need to recognize that even though our kids age out of the school system at 21, at 22, that learning cannot stop for them, so what are we going to do in terms of those continued interventions to make their quality of life as good as it can be?

And along the way, when we talk about these interventions, we're also talking about how do we uniformly collect data for what we do. And so perhaps we have outgrown a research matrix. It provides us with a snapshot of what's taking place, but what's behind that clearly needs to be a strategic plan that will set forth very specific goals, that will align those stated priorities with the review process and the funding and to be

able to get to the short, then the mid and the long term. Because if we just throw out the long term, it's more difficult for us on an ongoing basis to report back to our parents and for them to understand from us that we're only inching along.

We also need to assign those roles and responsibilities and identify funding and other resource requirements. As organizations, we have some ability to raise some funds, but we have the ability for resource and to gather resource that will help all of you once again to advance the science.

And the action plan that we're referring to here is a functional roadmap. It would be the kind of roadmap that when the IACC gets together, it's the roadmap that really sets the agenda, it's the roadmap that we will be discussing and that there will be integrated discussion and advancements that can be made. And the reporting that takes place will take place prior through perhaps the subcommittees, the working groups, that Tom has mentioned earlier and that we will be delineating

the parties who are responsible for carrying their respective charges, because we need to move this whole thing along.

And then we need to predetermine the systems for how we're going to evaluate our progress, how we're going to make those adjustments, and as I mentioned earlier, course corrections. So if we do all this, what's the benefit? Well, the benefit is that we're going to have some measurable progress. We're going to have progress that we can report on to our families. We're going to incent them. We're going to entice them. We're going to motivate them to stay with us, to bring their child and their family back in for more blood draws, for more evaluations, for more assessments. They will better understand the advancements that are being made, and they will want to be part of it.

And the collaborations and the opportunities for collaboration and partnerships through the groups that are represented here and also other foundations that exist, if we understand, once again in a strategic plan, what role each of us plays, then hopefully we will be able to get to

that goal and to secure greater funding also from the private sector.

And we hope that through the effective treatments and interventions that we will be able to build and sustain momentum so that we can someday sit around this table and finally understand what is autism and how do we stop it. Thank you.

[Applause]

Dr. Insel: Thank you very much, Denise. We're going to open this up now. What I think we'll do is at this point take comments from around the table. As I mentioned, we'll open up comments to the whole community through the website. And I think what we hope to do, based on the discussion in the next half hour, is to send out this document to the listserv and also to post the document so that people who are not in the room currently would still have a chance to contribute to any of the revisions.

So we're at that phase where we want to really answer two questions in the next half hour. First, from the IACC, is there something missing here?

Did this group get it right or not? Do we want to change or modify what's in this draft report? And then the second question is how shall we proceed from here? So on the first question -- did they get it right? Anything missing? Anything that they have.

Mr. Grossman: My recollection is that the last meeting 5 months ago or whenever that was, we had requested this. And I know personally one of the reasons I had requested it was not to find out in general had the autism field made progress on the wise goals set out by the roadmap 3 years ago but was to ask the very pointed question had there actually been any extra Federal dollars, any directed effort through RFAs, through grants requested, had there actually been any effort on the part of the Federal Government to bring us closer to realizing the goals as set out in the roadmap. And that is actually the one question that is not answered at all in this report.

So I would say to the extent that that question wasn't answered, then this report is incomplete, and I think it should be a living

document. One shouldn't get hung up in fads and factions in research, and one should be able to move and go where opportunities are. But that we come out of this with a recommendation to revisit the document in 5 months just isn't very exciting.

What would be interesting is to come out with a recommendation to direct more funds toward making it happen or direct different or propose different projects through the agencies and the guides to make it happen but actually considered action. And it does seem to me like there hasn't been that much in the 3 years directed from the NIH pertaining to the matrix and that the existence of the matrix didn't change the NIH funding pattern.

Dr. Insel: David, do you want to respond in terms of being at the meeting? Is there anything -- we didn't -- I'm trying to remember what discussion there was around funding per se or mechanisms. It was really focused much more on discoveries, putting together a research capacity, of trying to identify progress on each of those items but not progress measured in terms of

dollars, much more in terms of scientific accomplishments.

Mr. Grossman: I hate to be primitive about this, but it is one measure that we all understand. When the forms were put up there and said we measure progress by -- on the right-hand side it was like, you know, actual progress for our children as if to dismiss the other things, but in absence of actual progress for our children, measuring progress by dollars spent, new projects undertaken, papers published seems like a good method of measure. And for me, personally, what is missing from this report is a rating card on that. That was the actual question that I wanted answered when I asked for this report was what kind of new effort has gone out in order to make it happen.

And the other thing I would say is something that I know Ken has asked for, Autism Speaks asked for repeatedly at these meetings, is a better system of accounting to allow us to truly have a transparent accounting system and see what is spent on the disorder. And it would also help

evaluation tremendously and been waiting quite a while for that.

Dr. Insel: Denise, were you going to respond?

Ms. Resnik: I was going to respond to the progress rating sheet that was distributed, and that was specific to what is on the matrix. And I don't recall any discussion on funding or new initiatives.

Dr. Insel: There was an attempt, I think, to pull together manuscripts, publications on each of the initiatives, but I think that was mostly to support the claim of progress. But I don't think there was any consensus -- I'm not even sure we discussed it around the table with the people at the evaluation -- that money itself was a proxy for progress.

Dr. Ann Wagner: Can I just add the people who did the evaluation did have lists of new projects and things to look at. So you're right, we didn't really discuss it much, but it was provided in the background. They had a list of grants, new projects, new initiatives, and things like that.

Dr. Insel: One of the ways, though, and I

think we've gone -- I don't want to reinterpret what you're saying -- but I think the word that comes to mind when I here you talking about this is “accountability,” and I think that's really what Denise is talking about going forward is that if we recognize that, in fact, on many of these goals the NIH may not be the major source of support, and that's fine. But we need to know who's going to do what and who's going to be accountable for these going forward.

Mr. Grossman: That's news to me because the matrix was -- this roadmap was a major -- it was the focal point of a giant meeting 3 years ago. It was presented with great fanfare as an NIH product.

Dr. Insel: Jon, specifically, if you look at the congressional language, it actually specifically says that this is for public and private efforts, hopefully working collaboratively. Never made this a charge specifically to any part of the public effort. It was actually very clear, the language, that this could be done as well by private entities. And if

you look at how certain areas of research are funded currently, I must say at least within genetics, there's probably more money going out through some of the private groups than are going out through all of the public groups put together.

So I'm not saying that as a criticism. I think that what we have to recognize is that where we are now in 2006, as we begin to plan this out for the next year or 2 or 5, as Denise says, we have to bring all of those people around the same table. It makes no sense for us to have a meeting on funding genetics without having the Simons Foundation, which is pledging $100 million dollars to do genetics in autism, as part of the discussion. As we think about these workgroups and the implementation of this, it ought to be all of those partners at the table figuring out who's going to do what and how all that's going to be integrated.

Other comments or questions? Gail?

Dr. Houle: A comment I had is that, and this relates probably to the original matrix and maybe is something to look at in any reevaluation or

development of a strategic plan, and that is where under a matrix like this, even though it is titled "research," where would the services area fall? There still are some needs to identify further under the area that the NIH might call something like services epidemiology or who's getting services, what are the service preferences, how can we predict the service needs in the future. So if we talk about retooling or enhancing or developing a strategic plan, I just would want to suggest that that be considered as an element.

Dr. Insel: Other thoughts about that? Lee?

Mr. Grossman: Well, there's a couple of comments I'll make about the matrix in general, and I guess I want to come out in support of what Jon has mentioned, that the responses that we're getting in terms of the amount of money that's going in to support the matrix, it's unsatisfactory to me. It just doesn't cut it.

I think that there, at some point, even though there is more private funding coming into this now, that there has to be an equal and certainly a much greater commitment done by the Federal

agencies or Congress, et cetera, and that there has to be a much more rigorous approach to putting -- I think Jon said this the last time -- putting more gas in the engine. And it just doesn't seem like it's happening. It's hard to understand really what is being funded and what's not being funded at certain levels, and I think that that needs to be corrected.

A couple of other comments I'll make about the matrix is that in terms of prioritization, I think that there's a lot of efforts that are coming to the fore now in terms of environmental health issues, and for me personally, I look at this as a mechanism to get us closer to some very effective interventions and treatments. And from a money perspective, I guess, if we're going to put it in those terms that I'd like to see a much greater emphasis and priority and focus on those areas.

And then, lastly, there's this whole service function here. Services are kind of mentioned in the matrix. And again, going with what Gail said, and I have to apologize for many of us coming late because we were having a Services Subcommittee

pow-wow, and it was pretty much the conclusion that the matrix does fall short on the services side. The services side needs to, in terms of research, is very much needed. At the end of the day, that's what's -- anything that comes through in medical research is going to need this service model to deliver it. And also by putting a renewed emphasis on the services side, we'll be able to start delivering treatments today.

Somehow, at some level, it almost needs to be pulled out of the matrix and just be reemphasized within it and reincorporated in it, because right now it's just hidden. Also, with that said, I guess when it comes to the services, I think that if there is a renewed emphasis placed on services within the research matrix, and it is shown to be of such a high priority by this body and in word within the matrix, that there will be a flood of money that will come from private foundations and institutions into the service arena. And again, looking at that from what my immediate needs are with my own family, that's where I'd like to see major emphasis placed.

Dr. Insel: So as I look at what Denise has presented, there are these three workgroups going out the door, etiology and pathogenesis, diagnosis and detection, that's the second one and the third one was called interventions. Is the recommendation that that becomes interventions and services research or some program in there that would look at research that will inform policy? I don't know whether you want to call it implementation research or services research, but something on that axis, which is currently mostly missing from this document. Would that work?

Ms. Blackwell: It sounds reasonable to me. I agree with Lee, and I agree with your suggestion that interventions doesn't cover services. It's a little bit misleading, when I heard Denise talking about her son being in a supported employment program, to us, that's a service that we provide. I mean, I guess it's also an intervention, but again, it's misleading.

Dr. Insel: So the distinction here, though, would be the kind of science that needs to be done on services, like, we could call it services

epidemiology that would help to inform practice. If you knew, for instance, what most Medicaid recipients were actually receiving in the way of services -- that is a scientific question that we have a whole approach to, that we do that in other areas of medicine. And it could be developed here. It hasn't been developed except in a fairly small way for autism.

Mr. Grossman: In our discussions upstairs -- I guess downstairs -- over lunch, in the Subcommittee, we did discuss this aspect of science to treatment or conducting research that would influence legislation. And Agnes Rupp, if she's here -- did Agnes come out -- yes, I'm outing you, Agnes -- I think had some very good thoughts if you could perhaps comment if that's appropriate.

Dr. Insel: Why don't you do that for her?

Mr. Grossman: Well, basically there is a whole component of doing research that would show what the true economic burden is of this condition. And in that, we would then have, again, more power, more data to go and influence legislation, because

in the relative nature in many people's minds, it's a relatively low-incidence condition that exists. I certainly would argue that. But in terms of the economics and realities of this condition, it is a true national emergency.

Dr. Insel: So I'm hearing two additions to what the document that we've got, one that focuses on dollars so there's some sense whether there's been a delta, whether there's a change in resources over the last 3 years and how those resources have been deployed, and the second is to add something around services, services research specifically, and to put that in with some of the intervention pieces.

Anything else that's missing? And then we'll go on to talk about next steps, but anything else that you think should be in this document or should not be in the document as you look at it? Lucille?

Dr. Zeph: In looking at it and listening to the discussions this morning around need for personnel to be made aware of various aspects, either interventions or generic providers

understanding how to provide their services to individuals with autism, it seems to me that we don't have a really good handle on what it's going to take to make a difference there, that is, what is the knowledge base in terms of what do pediatricians know now, what do we need to do, how do you really -- and I see this as a research issue as well as just an implementation -- that is, you know, what is it going to take to move forward and tackle the issue of residency training, and this is just in the medical arena but also getting into various allied health, communication, education? What are the needs? What do people need to know, and what are areas that need to be conveyed, and what are systems and models for doing that?

Now, we may know this, but what we don't have, and it goes back to the economic issues; we need to have, I think, an overall better picture, and I put this under the guise of research, because it's the only way we're going to be able to put those data forward to Congress in terms of making financial requests. What is it going to take to

meet the need, and if training of professionals is a big piece of that need, how are we going to -- what is it going to take, whose responsibility is it to provide for those resources, and what are we asking for?

I think that Jon's point about the bigger research issue and how much money we're putting in is one that we really have to take seriously. You know, we have the reauthorization of the Children's Health Act, and my question is do we get what we need from that and is there a bigger ask that needs to be put in for that question? And if it's not necessarily just the biomedical research but it's the whole implementation of the findings and being able to make a difference, if those data never get implemented in any way that's going to change the quality of life for individuals with autism and their families, then we've wasted a lot of money.

So I think that, you know, somehow we don't have the entire picture, and we don't know what the cost is. What is it going to take regardless of what congressional subcommittee we're asking? I

think we need to know what the big picture is and what we're asking for, and I don't think that we really have a handle on that. I don't think we're getting what we need, but I'm not sure we have our hands on what that number is or what the subcomponents are to make this whole thing a reality.

And I really like the idea that you've put forward in the presentation of going back to what difference are we making anyway in terms of individuals with autism and their families? And that accountability piece that goes back to the people, I think, is one that we have to keep reminding ourselves of all the time and the various components that are going to be required to make that a success.

So I think we're biting off different little pieces here, and we're thinking of parts of the research. I like adding some of the service components to it, but there are systems components. There are financial components. And then the other questions that don't seem to be anywhere in there around issues of personnel and

implementation on the large scale -- what is it going to take to make a difference, so?

Dr. Insel: Thank you. Just to be clear, the purpose of this document is not going to be to implement votes in Congress, but I do think there's an effort here to provide the science that will be about service as it's now rendered. To give us a sense of what is the economic burden, the public health burden, what we call services epidemiology, who's getting what services and what is actually being done in the real world, what is having the biggest impact on function as opposed to just perhaps a change on a clinical rating, so all of that would be in this realm, which is actually mostly missing. So I think the suggestion is a good one that we can develop going forward, and there'll be an opportunity again to get additional input from a broader community, I would say, over the next few weeks.

In the time we have left, let's talk a bit about next steps, because we need your input about how we want this to play out. What are the action items here from where we are now, which is this

list of comments about the original matrix and some recommendations for changes; how do we take this forward? And I think what we're hearing from David and Denise is that we develop perhaps three workgroups that turn this into a living document. The groups would be highly integrated across both public and private partners, and there would be a charge to the groups that includes setting priorities, developing a list of who will be responsible for each item on the priority list, and then ultimately having a system of accountability for whoever is responsible. Is that -- if that's the plan? Denise, is that the way we want to go forward?

Ms. Resnik: I just wanted to add one other thing to what you said -- I agree with everything that you said -- and that is the quantifiable goals and objectives. And when you were talking about the presentation, which I thought was excellent, that we heard this morning with the American Academy of Pediatrics, you know, if we had identified or could identify that we want to train 1,000 physicians and primary health care

practitioners in 30 States in year 1, and, you know, 50 States in year 2 -- and then as an example, in Arizona where we were just successful in getting $9.6 million dollars for research and early intervention from our State legislature, we made that based on an economic impact argument. And when we launched our early intervention and physician outreach program, it was to get to 1,300 primary care practitioners and pediatricians in Arizona. But we need to look at numbers, and I think a big charge of these workgroups would be to identify, again, both the short- and mid-term and then long-term goals with quantifiable measures.

Dr. Insel: Right. So it would be taking what is in this document and really shaping it into an action agenda, which it isn't at this point. I think we've got comments about things that we need to do more of, some things that we've done a bit about already, but putting them into quantifiable goals is going to be the first order of business.

Did those three components, the etiology and pathophysiology being one, diagnosis and detection being two, and now interventions and services

research, is that the right way to cut this? People comfortable with that arrangement?

[No response]

Dr. Insel: Okay. Other issues about how we take this forward? The plan would be to move rather quickly. We'd probably give people about 3 weeks to get comments in from outside. We'll again send out this document broadly in the just the next couple of days. And then once we have comments in, we'll begin to form workgroups that will then report back to you in May. I never like to have the resolution of a problem being the formation of one or more committees, but in this case, I don't know any other way around this.

Because it's a big item here, I think we have to break it down. And to really turn this into an action agenda, we've got to have a few people who really run with it.

Any other thoughts about where we are?

Unidentified Speaker: Can I just raise a clarifying question? This is to review the research matrix, and you've included services research into that. I trust that does not negate

the need for the ongoing Service Subcommittee actually dealing with the issues of getting existing services expanded and approved and out there. I mean it sounded as if we kind of bundled it all into --

Dr. Insel: -- Oh, no, no, no --

Unidentified Speaker: -- agendas. I want to be clear.

Dr. Insel: I'm so glad you brought that up. This doesn't get you off the hook for a moment. No, the services agenda remains just the way it is, and there's a real need to take that to warp speed so that we get some of those items actionable quickly. This is really about finding a way to prioritize the science, figure out what we do next, or to use Jon's terms, you know, what do we want to invest in most heavily going forward and then also coming back and making groups accountable for those pieces that they've taken responsibility for? It's a good time to do this, because we've got lots of things rolling out through the ACE Network and others that we can have this aligned with hopefully. Coleen?

Dr. Boyle: Just a comment on the, I guess, etiology and pathophysiology group. I was trying to think of where our issues fall. And, honestly, they fall on both detection, diagnosis and etiology and pathophysiology, but that group, particularly for me, is a very complex group that crosses a lot of issues, and more so than the other two. So, you know, I'm wondering maybe we should perhaps in the first meeting of that group think a little bit more about its structure. Because I just feel like it would be hard to sort through all the issues that go into the composition of that group.

Dr. Insel: Yes, I agree. We talked about this briefly earlier in the week and, you know, we were trying to figure out how to cut this at the joint since somebody suggested this really might be a salami, that there's not an obvious way to cut this. But we just thought it was too broad to try to do it in one or two groups, and so three seemed like the right number. But if, for instance, epidemiology is, you know, which probably would fall, I guess, into, well, maybe diagnosis and

detection --

Dr. Boyle: What you're talking about is health sciences research, opponent of epidemiology. You know, I mean, it goes across the spectrum, but obviously etiologic epidemiology or analytic epidemiology fits into, like, our CADRE project. It would fit into the second group.

Dr. Insel: Into the second group, right. And that's the kind of --

Dr. Boyle: And I'm not trying to think so much for CDC per se, but I just think of that as being a very complex area there in terms of very heterogeneous aspects, both in terms of disciplines of science as well as different processes.

Dr. Insel: I think that it gets complicated when you try to nail this into one category or other, but I think once the groups form, that critical piece will be to identify, based on what we've done so far, what are the chunks that need to get prioritized. And in this case, I mean, it's a good example where, for the most part, epidemiology is going to be within the CDC

umbrella. That's where it will be done. That's not something that NIH has done much of.

And I think we just need to be clear about sort of taking different pieces of what needs to get done fairly quickly and figuring out who will be responsible for each of these pieces. And in some cases, it may be more on the private end of the spectrum. In some cases, it will be one public agency versus another. But for any of us who've started to look at this, there's a real need to come up with a plan that actually tags to individual agents that are going to champion an area and to know how that's going to happen. Lee?

Mr. Grossman: Yes. I have the same question with environmental health issues, where that's going to fall, because it could be crosscutting and --

Dr. Insel: yes. I thought the discussion that we'd had so far was that that's around etiology and pathophysiology. But, again, you could argue that it fits into the Phenome Project and a bunch of other areas. I don't know that we need to get too hung up about which of the three categories as

long as the areas are covered and the appropriate people are at the table so we'll know who's doing what.

Final comments about this? So we have some additional suggestions. We'll be open for business to hear yet more suggestions from a broader community. We want to also move fairly quickly to get groups together to actually push this along, and we'll be consulting with you about getting you back to do that. As we've heard from people who were part of the panel, there was a real sense that this needs to be a living document. We don't want to wait 3 years before it gets revised again. This should be an iterative process, lots of input, and with each new discovery, the plan should change. That's really the best way to do the science.

So going forward, we'll look for a lot more feedback on this. We'll plan to take some of the May meeting to inform you about progress, and many of you will be involved in parts of this. Hopefully, over the next 6 months, we'll get to the next stage of what we'll call -- I don't know

if we'll call it Matrix 1.5 or 3.0, but it will be something very different from that multicolored rainbow thing that we've been working with up until now. Jon?

Mr. Shestack: I just think that when we suggest going forward that economics be part of the evaluation process. I'm sure the private groups would be happy to, in the partnership, say how much money they're spending in certain areas. But it would be useful for all of us if the NIH would do it as well. It should have been done retrospectively, but let's do it going forward as part of the evaluation process of the matrix if it is a living document to show us how we are doing on reaching these ever-changing goals. Thank you.

Dr. Insel: I think that's a message that many people have been nodding their heads about, so we hear that message very clearly. Okay. Let's take a no more than 10-minute break. David Schwartz has just joined us, and he'll start off at about, let's say 2:45, to talk about NIEHS.

(Whereupon, a recess was taken from 2:29 p.m. until 2:39 p.m.)

Dr. Insel: I'm going to begin the last session on environmental issues and gene environment initiative. Before we start, I wanted to just finish one more item from the previous session. I was remiss in not pointing out the huge amount of work that it took to put this evaluation together. There were many, many people within the NIH who worked on this, but most of all, two people from NIMH who took the largest share of the burden of labor, and often kind of in the last minute, because we started on this very late -- Marina Volkov, who's here, and David Zielinski, who's in the back, if you'll both just put up your hands? Thanks for everything you did to make this possible, and I'd like to say that you're finished, but now it sounds like we're only part of the way into what will become a long-term project, so thanks for getting us to this point.

It's a pleasure to introduce Dr. David Schwartz. David is the Director of the National Institute of Environmental Health Sciences, NIEHS. It's one of the 27 Institutes and Centers at the NIH, and it's distinguished in many ways, not the

least of which is that it's the only one that doesn't live here in Bethesda. It lives in North Carolina where David has his base. He, as Director, oversees the Institute's comprehensive research portfolio of both basic and applied research to reduce the burden of human diseases that are triggered by the environment. And he, in that role, not only runs the NIEHS, but he runs something called the National Toxicology Program, which is an interagency program to test chemicals and other agents of public health concern.

Just a little bit of background. He came to NIEHS from Duke, where he was a Vice Chair of Research and Director of Pulmonary and Critical Care Medicine. He played a pivotal role there in establishing three interdisciplinary centers in environmental health sciences, environmental genomics, and environmental asthma. So he's got a long-term commitment in developing state-of-the-art technologies to tackle critical and individual public health issues. David thanks for joining us. I know it wasn't easy getting here from North Carolina today, but we're delighted you finally

made it.

Dr. David Schwartz: Thanks a lot, Tom, and thanks for that really very generous introduction. Where did everyone go? The room was so packed when I came in. Are there people in the hallway that need to come back?

Dr. Insel: I could draw out this introduction a little more if that would help. I think they were waiting for me to finish, and they'll come in at that point.

Dr. Schwartz: Well, it is a pleasure to be here, and I had been looking forward to this this entire month really, because this issue of autism is an issue that I've learned about over the past year and a half. It was not something that I knew much about before I came to NIEHS. And I learned about it not only through Cindy Lawler, who is our lead person at NIEHS, and also not only from Tom, but I learned about it from the advocates in the community in what I would say has been a very collaborative, interactive, positive process that allowed me to understand the disease better, allowed me to understand the issues more

critically, and helped me to understand the importance of environmental sciences as it relates to this disease process.

So this is something that we have a lot of interest in at NIEHS, and we would like to work in a collaborative way with the rest of the matrix, whatever the matrix is -- it sounds like a pretty scary name -- but with the rest of the matrix to try to contribute to this very important problem.

So what I prepared today was to just give you an idea briefly of what we're doing at NIEHS but, more importantly, what we plan to do with the genes and environment initiative and how that relates to the autism program. So when I think of autism and the problems related to autism, there are three critical questions as it relates to etiology. The first is what are the relevant exposures and genes associated with autism? And these questions are obvious to everyone in the room. The second is how do these genes and environmental exposures interact with each other? And, thirdly, does this relationship between genes, environment, and autism tell us something

about the biology or phenotype of this disease process? In other words, oftentimes as clinicians we think of a disease as a disease, but when we learn more about it etiologically, we understand that there are lots of different phenotypes and lots of different lessons related to the biology of the disease that we would not have known had we not known the etiology of the disease and the complex etiology of the disease.

And I think autism is probably a very good example of a complex disease that's likely to be caused by multiple environmental, multiple genetic factors, interacting in different ways and may be causing different subtypes of the disease process. Certainly it's an open question to understanding whether elements of the etiology will help us understand issues related to the biology and the phenotype of the disease.

So as Cindy would point out, there are a number of things that we're involved with at NIEHS and supporting at NIEHS, from very basic studies in animals and developing animals of this disease to epidemiologic studies. And I'm really very

proud to say that we just approved funding for the CHARGE study, which is a large epidemiological study. It began as a pilot developmental study in 2001 and now is a full-blown, population-based epidemiological study looking at the environmental etiology and the genetics of autism. We're supporting it at about $7 million dollars over the next 5 years, so this is a study that you'll hear more about as it matures.

But what I'd really like to talk about is the Genes and Environment Initiative and the importance of this initiative as it relates to autism, because this is something new at the NIH. This is a trans-NIH initiative that began this year and will continue for the next 4 years. It's funded by all the Institutes at the NIH for a total of $192 million dollars during the 4-year period of time, and it basically has two components, a genetics component that will appropriate approximately $104 million dollars, use approximately $104 million dollars, and an exposure biology component that will be funded at about $88 million dollars during this 4-year

period of time.

Let me first tell you about the genetics program. The genetics program focuses primarily on genome-wide association studies, but focusing on genome-wide association studies in complex diseases in autism, it brings up a lot of other issues in terms of data analysis as well as translation of studies to understand the functional aspects of the genes that are identified. Let me just first say this is a coordinated effort across the NIH. All the Institutes are involved in this Genes and Environment Initiative, and these are the individuals that are on the coordinating committee: Frances Collins from NHTIR and I lead this effort as co-chairs of this committee, but really all the Institutes contribute in a very meaningful way to this new initiative.

So the genetics program consists of several components. The largest component is the genome-wide association studies that result in identification of loci in the genome and genes that might be involved in these complex diseases.

One can move very quickly identifying a locus to identifying sequence variation within those loci that are related to complex diseases, then functional studies and translational studies to try to understand what the biology is that underlies this association between genes and genetic variations and complex diseases. So as part of the genome-wide association studies, which I'll talk more about in just a little bit, we're supporting a variety of different focused efforts to look at specific diseases that are complex in nature caused by multiple genetic and multiple environmental factors -- could be autism that we end up supporting. It could be diseases like asthma or cardiovascular disease or diabetes. There are a variety of diseases that could be supported, and the choice of which disease will be supported will depend on the review process of what investigators -- which projects are put forward and which are reviewed to be the strongest application of this technology to study a particular complex disease.

Within the genetics program, there's a data

analysis issue that's going to be across the genetics program. It's not particularly easy to look at 500,000 markers across the genome for a particular disease and sort out which genes or loci are associated with the specific genetic disorder. Likewise, there'll be data-basing problems that will be addressed as part of the genetics program. As I said, the large percentage of the genetics program will focus on the genome-wide association studies, but substantial components will be dedicated to find mapping, sequencing, and functional studies as well as translational studies.

The genome-wide association studies have already been initiated. They've been initiated in terms of a release of an RFA that will support the investigation of 15 different diseases over the next 4 years. They'll support genotyping centers, coordinating centers, and disease-specific studies that are, again, complex diseases, diseases that can only be sorted out if you look at the entire genome and you ask the question, Which of many different genes could be contributing to this

process?

The second component of the genetics program is data analysis and sequencing, and that will begin subsequent to the genome-wide association studies.

And the third component is this functional component or translational component to identify the biology that underlies these genetic associations.

The program that I want to discuss in a little bit more detail is the environmental biology program. That's a program that NIEHS is taking the lead on, and it focuses on developing much more personalized measures of exposure that we think are related to the risk of developing disease. So, in other words, we're interested in developing measures of exposure that are precise, that are sensitive, specific, and individualized so that we can discern differences in diet, physical activity, environmental exposures as well as psychosocial stress and addictive substances from one individual to the next in an investigation, so that with the kind of precision that the genetic

studies have, we want to apply a similar degree of precision to the measurement of environmental exposures that we think are important in terms of the risk of developing various diseases.

If you think about the exposure measurements that we currently use and apply to many of the studies that you're familiar with, especially as they relate to autism, they are either area-based studies, not personalized, or they're retrospective assessments of what someone thinks they might have been exposed to in terms of a dietary history. In no way at all do they approach the precision of the kinds of measurements that are applied to genetic studies.

So if you think about the spectrum of when someone first gets exposed to when they develop disease, there are various points along the way that are measurable. For instance, thinking about the internal dose, the Centers for Disease Control have already developed a series of body burden measures of exposure to toxins and toxicants in the environment. In fact, if you look at one of their very recent publications, you can see that

they've developed close to 150 different measurements that reflect very clearly body burden measures of exposure. However, the problem with body burden measure of exposure is that you have to catch them at the right point in time and that, from individual to individual; they may vary quite a bit in terms of where the substance ends up being deposited in the blood, in the serum, in the urine, in the fat. It's hard to get at these samples, and because of genetic variation from one individual to the next, it might be quite variable in terms of the rate of deposition.

So what we've chosen to focus on in the biology exposure program are two measurements -- one, personalized environmental sensors, and then biomarkers of response and biosensors of response that will allow us to assess whether a system has been perturbed in such a way that places an individual at risk of developing disease. So let me just be a little bit more specific about this. The exposure biology program is, as I mentioned, a 4-year program. The reason that I have 2011 here is that it's very likely that this program will

take more than 4 years to mature. And we're hoping that this program can continue well beyond 2010.

It's got essentially four components to it. The first component is one that focuses on environmental sensors, personalized sensors, the development of devices essentially that people will wear that will allow us to measure differences in diet, physical activity, chemicals, and biologics that they may come in contact and psychosocial stress and addictive substances. And when you think about the way electronics and microprocessors have developed, it's very likely that we'll be able to accessorize individuals so that they'll be able to wear very small devices that will allow us, in discreet detail and accurate measurement, to assess a variety of different exposures. And this is what those RFAs are focused on, and we've already released three of those RFAs focusing on those different device.

The secondary development is in biomarkers, biological responses, biological fingerprints that tell us that a system has been perturbed, a system that we know that may be important in terms of

disease development, may have been perturbed like inflammation, oxidative stress, program cell death, or even epigenetic markers that tell us that something has gone awry in this system that may place an individual at risk of developing disease, may relate to an environmental exposure, or may relate to an endogenous form of stress. In some ways it's agnostic to the exposure that someone's been exposed to; it tells us more that there's been a biological response. It obviously interfaces very clearly with these environmental exposures.

In terms of these biological responses, we're also focused on the development of deployable devices that allow us to measure biological responses so that they can be incorporated into epidemiological studies. And, ultimately, we want to use these environmental sensors and these biological responses in the genome-wide association studies to look at gene by-environment interactions.

This is the distribution of the percent of the funds that we have, the $88 million dollars that

we will allocate to this over the next 4 years to each one of these activities. And when you think about the two components of the program, it's very clear that there's a third component of the program, which is to look at the relationship between genetic variables and environmental variables in terms of the risk of developing complex diseases.

Now, how does this relate to autism, and how could autism benefit from the Genes and Environment Initiative? There are several ways. The first is that the disease itself could be chosen as one of the diseases to study in the genome-wide association studies. This will depend on who competes for the funds that are available, whether proposals are submitted to the genome-wide association studies group that focus on autism and whether they are scientifically rigorous enough to rise to the top in terms of the scientific importance and strength of the proposal.

The second way is that the biomarkers of response that we develop could easily be applied to ongoing studies by using bio-samples that have

already been collected and stored in a variety of autism studies.

The third approach is that these new environmental sensors could be used very easily in future studies to identify how diet, physical activity, psychosocial stressors, and a variety of environmental stressors could, in fact, alter the risk of developing autism.

And the last is that there are a variety of new tools that are going to be developed in the Genes and Environment Initiative in the way of analyzing and categorizing gene and environment interactions that could be very relevant to studying autism.

So with that, I'll open it up to discussion. I really look forward to your questions and would like this to be a back-and-forth dialog. Thank you.

Dr. Insel: Thanks very much, David. We've got some time for questions. Yes, go ahead.

Dr. Pazin: So you indicated an interest in following epigenetic markers, and, depending on how studies are designed, epigenetic phenomena

could appear to be environment or genetics or both. Is that left to the investigators how they will do this? Are you going to be specifically looking for epigenetics initiatives?

Dr. Schwartz: We have included the language of epigenetic markers in the RFA related to biological response indicators and also the centers that we intend to support in terms of the development of biosensors and related to biomarkers, so we're very, very interested in supporting the development of more rapid approaches and more field-deployable approaches to looking at epigenetic markers. Currently, it's a very cumbersome assay, and there are very few standards in the field, so this is an area that we think, with the right group of investigators and enough support provided through the environmental biology program, we will be able to help accelerate the development of this field in terms of more generalizable approaches to looking at the importance of epigenetic changes in the development of disease. Now, as you point out, that won't tell us necessarily what the cause of

the changes in those epigenetic markers are, but it will define that epigenetics and epigenetic changes methylation or changes in histone regulation. Methylation of CPG motifs or changes in histone regulation may, in fact, be important in terms of the risk of developing a disease.

Dr. Insel: David, when you think about looking at exposure burden, what advice would you give people around the table who are involved with long-term studies or any kinds of studies, let's say, of the Phenome Project for autism? What should they be collecting now that they'll wish they had in 5 years? Is it hair or skin, or is there some biological sample that may prove to be very informative that we should all be thinking about in a consensus way?

Dr. Schwartz: Well, you know, I think that at this point, the question related to bio-samples is how much can you afford to store, because I think that many of the samples that you'll be able to collect will be important and valuable in the future. So certainly DNA is a no-brainer at this point. It's important, I think, to store some RNA,

and I think it's important to figure out what sample of RNA would be most important to store for the disease that you're looking at. I don't know if peripheral blood RNA makes sense in autism, but some aliquot of RNA does make sense. I think that it probably is the most logical specimen, peripheral blood RNA. I do think that nail specimens would be important.

They've proven to be important in the nurse's study, and there are a lot of nutrients that are deposited and can be assayed in nail specimens. The problem with going beyond that and saying, you know, store serum specimens and urine specimens, the question is well, how do you store them and when do you collect them and under what circumstances do you collect them? Is this a fasted specimen that you get, or is this just any specimen that you obtain? My view is that a lot of variables can markedly affect those types of specimens, and I've seen affect those types of specimens, so I think that you have to figure out some sort of standard way of collecting those specimens that decreases the likelihood that

they're going to be altered by what's happened in the last 12 to 24 hours to that individual, whether they were exposed to some secondhand cigarette smoke or whether they ate a high-fat diet the night before.

I don't know about hair. You know, I find that to be somewhat problematic. It's said to be useful in heavy metal exposures. I've not found that to be the case in particular. It can be contaminated by lots of things in the environment, so I think it becomes somewhat problematic.

The best folks to ask that question to are the people at the CDC who have developed this panel of markers that they rely on and know how to use in terms of these body burden measures of exposure, these 150 markers that they've developed, so Larry Needham at the CDC could answer that question very, very easily within the context of what he's currently able to measure.

I think that, you know, what we're thinking more about is what are the dynamic measurements that tell us more about biological pathways of response? So I'm not necessarily looking at just

proteins, for instance, in the blood but looking at proteins that are phosphorylated or have cysteine residues as a way of looking for evidence of oxidative stress. In some ways, we haven't even yet developed the assays for that, let alone to know how to collect those specimens and what exposures or what events might alter those specimens.

So I think the most simplistic answer to your question is we could easily find that out from the folks at the CDC, but I don't think that that's necessarily going to be comprehensively helpful for what we want to do over the next 3 to 5 years. We're going to learn a lot of the next 3 to 5 years in terms of what new specimens need to be collected and how they need to be collected.

Dr. Insel: Other questions?

Dr. Schwartz: There's a question behind you.

Dr. Insel: Yes.

Dr. Trepagnier: In various subfields of medicine like oncology, and to an extent, psychiatry, there's intentional exposure and an interest in the interaction of treatments, in

other words, and genetic makeup. To what extent will you be interacting with people who are -- you know, with studies on these somewhat similar missions?

Dr. Schwartz: So to what extent will we be interacting with whom? I'm sorry?

Dr. Trepagnier: Well, people who are studying the relationship between various psychiatric or cancer treatments and genetics of patients. It strikes me that looking at the interaction of, you know, unintentional exposures and genetic makeup is just analogous to looking at the interaction of intentional exposures and genetic makeup, so what sort of interaction will there be among groups who are looking at these similar types of problems?

Dr. Schwartz: Yes. You know, my view is that we have interacted with those groups before, and we'll continue to interact with them. In fact, we've supported a lot of those groups that are looking at how intentional exposures, whether they be intentional environmental exposures or intentional -- not intentional -- but unintended occupational exposures -- how those affect human

health and disease and how they interact with various genetic factors that might enhance or decrease the risk of developing a response, so absolutely. In fact, we're developing a clinical research unit at NIEHS just to do that, to expose individuals in different ways so that we can understand how underlying genetic changes might affect the way they respond biologically to an environmental agent.

Dr. Trepagnier: So the techniques, the bioassays, the sensors, that will be shared information?

Dr. Schwartz: Yes, absolutely. In fact, you're asking even a bigger question, which is that, you know, there is a whole industry that's already developed in the biodefense in terms of the development of these biosensors and environmental sensors, and we're interacting very, very closely with those groups that have already developed very sophisticated assays and measurement tools that could be directly applied to the questions and the concerns that we have.

Dr. Insel: Okay. I think given the time, we

should march on. Thank you very much, David. Larke, did you have --

Dr. Larke Huang: Yes. I thank you for your presentation, and this is very complex, a little bit over my level of research or my area, but I'm curious how in light of the previous discussion we just had on the research matrix you can speak to how you move this into interventions or implications for interventions or services?

Dr. Schwartz: That's a great question. So my view on this is that if you understand the etiology of something, then you can address in a very specific way what types of interventions might be beneficial and in whom they might be beneficial. So one could imagine that if we identified several etiologic agents, we would move to reduce exposures to those etiologic agents in individuals that might be genetically more susceptible or in the population in general if the risks were that generalizable. But in addition, understanding the environmental exposures that are relevant to a disease and understanding the genetics that predispose individuals to respond or

not respond to the disease will tell us about biological pathways that are important in terms of that disease. And even among individuals who have developed disease, we may be able to identify very novel therapeutic approaches based on what we learn about the environmental etiology of the disease as a way of intervening in a way that hadn't been conceived previously. So I would say, you know, there are at least three ways of intervening. One is simplistically decreasing exposure. Two is identifying those at risk of responding or not responding to the exposure. And, thirdly, understanding that tells us more about the biology that could, in fact, lead to very new and maybe even more beneficial treatments for the disease once it gets established.

Dr. Trepagnier: So, given this new research collaborative and this $192 million dollars, is that part of the research plan? Is that part of the portfolio of studies to do, start doing, this piece of it?

Dr. Schwartz: The intervention, no, is not part of it. No. In fact, if you think about what

we're undertaking in a 4-year period of time, we'll be fortunate if we accomplish what we've set out to accomplish in this 4-year period of time. And I think we're going to make a lot of headway during this next 4 years in terms of these environmental sensors and in terms of understanding the etiology of disease and in terms of developing new tools to understand the etiology of complex diseases in general. I think the interventions will come maybe in parallel with that. As we tackle different disease processes and identify who's at risk or what's related to the exposures, those interventions will fall out in parallel with the discoveries that are made in this program.

Dr. Insel: Thank you. We're going to have to move on. We're a little bit behind schedule. David, thank you very much for that presentation. We're going to move on to hear from Dr. Jeff Bradstreet. Dr. Bradstreet is a fellow of the American Academy of Family Physicians and a member of the American College of Toxicology. He's the founder of the International Child Development

Resource Center in Florida and is actively involved in treating children with autism. The title of his presentation, as you can see, is "The Role of Environmental Factors in the Pathogenesis of Autism." Thanks for coming, Jeff.

Dr. Jeff Bradstreet: Well, Thank you very much for having me, and I feel a little bit like I'm presenting to the Knights of the Roundtable on your noble cause to improve the world. I know many faces in the room, and I'm meeting some new people, some new friends, so it's a pleasure to be here. And for the Committee members, you have been given during the break the proceedings from the Environmental Factors in Neurodevelopmental Disorders Symposium that took place last year by SafeMinds, NAA, with the support of NHS. You've also been given a recent review of many of the environmental factors that were discussed at that meeting, and many of the scientists that were at that meeting are discussed within the context of that review, and then a video, if you choose to watch it, about children who are actually recovering from a disease that's supposed to have

no recovery. And that's an intriguing factor, and how do you define recovery, and how do kids get back lost function?

We're going to try and do this very quickly. I've been counseled several times about time, but as we think about the prevalence of this disease, it seems to be becoming extraordinarily prevalent, and when you break this down to numbers that I can understand, and I'm not an epidemiologist, and I never really enjoyed statistics, but 1 in 89 boys from the "MMWR" report of this year and 1 in 267 girls strikes me as being rather severe in terms of the number of individuals in our society that are lost. And if you look at a broader term of autism spectrum disorders -- I know the last one was just autism -- this is the broad autism spectrum which would include PDDNOS and things like that; in the U.K., it's nearly 2 percent of boys, 1 in about 54 boys. Oftentimes, you'll see statistics with autism presented as children. This is a male-denominated disease where four times more males than females are represented within the cohorts, so I think it makes sense to look at each

subset and define what is the real prevalence in each gender.

So where we come -- about $8.7 billion dollars a year to deal with methylmercury toxicology and the complications of that. This is in EHP. About 17 percent of children in the U.S. now suffer from a disability of behavior memory or the ability to learn, and there's been about a doubling of the amount of annual cost in billions for total neurodevelopmental disorders, so we're up to about, and I would say probably now, close to $200 billion dollars a year for neurodevelopmental in children.

And then as you can tell from the statistics in autism, a dramatically prevalent disorder, particularly in boys, that doesn't seem to have leveled off at this point in time, and it's a little bit scary where this is taking us in the future. Hence, the need for looking at environmental factors as carefully as possible, because many of us don't believe that we're in the midst of an environmental toxicological event that we might be able to influence the occurrences of.

This is the brochure from that conference or the symposium where many scientists got together, but the symposium largely centered around mercury as at least a model of a neurotoxicant that was well described and well understood in many ways, more so than some of the other more subtle toxicants that were out there. So while this is going to have a bias toward mercury, don't assume for a minute that I don't think other toxicants are probably at least as important or perhaps even more important once we learn more about them, so one in six children currently are born at risk for mercury intoxication. We have absolutely no plan for dealing with them at this point in time, unlike lead, where we have a nice screening program. We have detection; we have a lead-reduction program. It's really pretty much left out in the open at this point in time with no guidance for pediatricians about this.

The history or the meaning is such that in March of '05, SafeMinds, the National Autism Association, and Dr. Ken Olden, who was then the Director of NIEHS, myself, and another clinician

met to discuss our concerns about the environment and autism. Dr. Olden was very receptive and decided one of his parting gifts to the autism was to help to fund this conference and put it together to bring together toxicologists and other scientists interested n the environment, neuroscientists, and then two clinicians -- I was one of those -- to present our findings and observations. And as a clinician, I bring about 4,000 childhood experiences in autism over the last 10 years to bear. We have currently evaluated and at least attempted to intervene for about 4,000 children with autism between myself and a pediatrician and another physician that works with me.

The Environmental Factors Symposium took place in August of '05, and you will be getting the summary of those proceedings as you look through this data. So the scientists and clinicians reviewed the new findings, made recommendations, and essentially tried to put together a roadmap for the things that we thought would be helpful as you go forward in the environmental discussions in

autism. So this would perhaps apply to trying to fill in some of the blanks in those portions of the matrix. The presenters -- I'm not going to go through all the names but credible scientists from many well-established institutions that were interested in this discussion, and it was, I think, a very nice opportunity to think-tank and put together a roadmap. There were many participants from the Department of Health that were present as well, and almost all of them are in the room today.

Dr. Olden's brainstorming ideas, I think, are guiding principles that we should not lose sight of. Number one would be rapidly helping the most children, and the sense of time urgency is felt by many of us in this room who are parents. And I have a 12-year-old son named Matthew who is currently probably recovering from anesthesia after a traumatic event with a gocart where he managed to break out many of his front teeth, a little lack of judgment on his part. But he is a fully included 12-year-old in 6th grade, and the inclusion program for him has been extraordinarily

successful. He is doing 6th-grade-level work, where when he was 5 years old, his only contribution to the world was poop smearing and stimming constantly all day long, so that's, I think, a rather successful degree of progress for him which, I think, can be modeled by many of our kids.

Specifically, autism is a complex disorder with multiple biological things that are defined in the literature going wrong. That gives us avenues to potentially address as clinicians. Assessing the potential contribution from environmental factors to autism as a causal or at least an exacerbating agent was one of his guiding principles and then framing autism as a potentiality treatable disorder, and I would say further as a biological disease where it is currently now considered either genetic or psychological.

This is the review, and those of you who don't have this, I would encourage you to seek this out, and this is from the "Journal of Toxicology" in 2006 from folks in the Psychiatry Department at

The University Texas, and it goes over many of the things that were discussed in detail at the symposium, although this is not directly from the symposium. And to go very, very quickly through the highlights of the presenters and their publications -- however, I would say that in the process of getting peer-reviewed science into good literature when you're talking about mercury and autism in the title is extremely complicated and difficult, so for those scientists who have been able to publish in this arena, I certainly give them a lot of credit, and it's a tough peer-review process for sure.

This is from Mark Blaxill showing a time-trend analysis that looks very scary for those of us who are concerned about where we're headed with this, because as you can see, the arrow would appear to be pointing straight up on many of these graphs.

This is from Dr. Hornig and her group at Columbia, and I think she developed an interesting model of the postnatal effects of thimerosal in the mouse. Now, again, I'm very much aware of the thimerosal epidemiology in autism, which shows

that there's no correlation between autism and doses of thimerosal, and I'm not going to get into a debate of whether that's good epidemiology or not. At the very least, mercury is a model that we can look at as a way to study neurodevelopmental disorders.

And Dr. Baskin, a neurosurgeon at The University of Texas -- excuse me -- at Baylor College of Medicine in Texas -- showed that very small doses of thimerosal completely disrupted both neuronal activity and those of fibroblasts as well, indicating that if small amounts of mercury do make it to the brain, their effects on development would presume to be significant.

And this is from Holmes, Blaxill and Haley where there was an inverse relationship between the severity of autism and the amount of mercury in hair, and I would absolutely agree with Dr. Schwartz's comments that hair is not necessarily a reliable indicator of heavy metal exposure, but the trend analysis was pretty interesting in that for first baby haircuts anyway, the worse the autism, the less the mercury was in hair, and the

presumption is that that means that they are poor excreters or ethyl deficient, cysteine deficient, and can't actually excrete the mercury that they're exposed to.

And Dr. Dietz showed that very tiny amounts of thimerosal, which is ethyl mercury, completely disrupted the growth factor in neurons and dopamine transmission and obliterated methionine synthase, which is critical to the management of the methylation transulfation pathway.

And in the comparison of what happens to inorganic mercury and organic mercury from different sources has been very articulately put together by Tom Burbacher and his group working with Tom Clarkson, who's a noted mercury toxicologist. And, essentially, if inorganic mercury makes its way into the brain or organic mercury makes its way into the brain and then becomes inorganic mercury, which is the normal process, it never leaves. The half-life is not calculable because it's too long.

And this is work from Charleston where they looked stereotoxically at the brain and found that

exposure to methylmercury in activation of microglia, which will be a topic of much discussion, I think, in years to come as what's happening to the immune system, the intrinsic immune system in the brain, becomes more and more important to those of us that see immunotoxicology as a both etiology and potential avenue for intervention.

So mercury and autoimmunity -- this is from Ellen Silbergeld who's here at Johns Hopkins -- or nearby at Johns Hopkins -- who finds that not only is mercury a direct neurotoxicant that's well described, but it's an immunotoxicant which alters the function of the immune system in fairly predictable ways and in many ways may model what's happening with what we see in autism.

And then I would agree that these somewhat retrospective database analyses looking at atmospheric exposure or atmospheric emissions in mercury have a lot of things that you can pick on that are potential weaknesses in the studies, but they're intriguing. This one was one of the scientists who presented, from Dr. Palmer at The

University of Texas, who found that for every 1,000 pounds of mercury that goes up a Texas smokestack, there's a 61-percent increase in autism in that State. And that's an interesting observation, but it was later confirmed in a similar way from an environmental analysis from database exposures within the San Francisco Bay area by Windham and her colleagues that showed that, again, the number-one correlate was exposure to mercury in terms of the risk of autism.

This is our case-control study of mercury burden in autism, and I would say relative mercury burden. And we gave children a provocation exposure to DMSA, which is a known mercury chelator, and we used neurotypical controls of parents who wanted to have their kids evaluated. And depending on how you subtype the groups on vaccine exposure or lack of a vaccine exposure, we saw between four to six times more mercury after a challenge in the autistic population.

And this is a very intriguing new bit of data. This was not presented at the conference, but it's so important that I wanted to go over it. This is

from Dr. Woods and his group in the University of Washington. It shows that there's an excellent biomarker, and that is the keto-siococporphyrm and that is a specific porphyrin that shows up really only with the exposure to mercury. We don't know how long it stays positive after exposure, but it's presumed to be a fairly acute marker, and we are about to undertake some sophisticated, both porphyrin analysis as well as genetic analysis, with Dr. Woods' group. The funding has been approved by the University, so that will take place and probably done in about 3 months. We should get some good data out of that.

We're going to be looking at both CPOX forging and BDNF, which, in previous publications, have been shown to be mercury vulnerability genes.

And this is some recent work from Dr. Nataf in Paris, France, that showed a very significant increase in the excretion of atypical porphyrin, specifically the mercury-related porphyrins in the children with autism and also showed a reduction in those porphyrins following DMSA chelation. And it's nice to see some of the folks from NIH who

are going to be looking at DMSA and autism here. This is at least some confirmation that clinical observations along those lines are being reproduced by other investigators.

Mercury is a global problem. It doesn't really matter where you live. If you live near industry, if you live near civilization, you're going to be exposed to mercury in some fashion. And then Dr. Choi from Harvard presented the work that has been ongoing for a long time, basically outlining that prenatal exposure to methyl-mercury is a significant neurobehavioral problem that appears to be permanent, although none of these children were attempted to be intervened and chelated to see if that would change over the course of time.

Dr. James has looked at oxidative stress and finds it to be prevalent, and the things that would defend against oxidative stress, which is the sulfation and methylation pathway, are significantly deficient in children with autism. Specifically, glutathione has been noted to be deficit. Glutathione is the main intracellular antioxidant, and the reduced form of it, which is

the true defender, is about half of what it should be in the autistic population compared to controls. And this just shows that biochemistry can be colorful for those of you that are not necessarily biochemists.

We went on recently with Dr. James to publish our metabolic endophenotype and related genotypes in autism, which show a very clear pattern of vulnerability, toxic stress, both biochemically as well as genomically.

And Dr. Herbert presented with a very interesting discussion about autism a brain disorder or a disorder that affects the brain, and I would say that could change the way you frame your research and you frame your discussion of this disorder, and I would hope that you would keep that in mind as you move forward.

Dr. Vargas' group form Johns Hopkins presented their data on neuroglia activation and, in fact, described it as neuro-inflammation, which is still controversial. Some of the other neuroglia scientists that were there said maybe this isn't inflammation, maybe we should just leave it at

activation and then discuss what's really happening with the glia and how they're responding. Is it repair? Are they the agents of destruction and damage? And I think that's an area that we'll know more about in the near future, but microglia are clearly, markedly activated. What that activation means is unknown at this point in time, but an area that is hotly being pursued by many scientists. Is it a central mechanism in autism? In our clinic setting, we assume that it's an active issue in many of the kids that we see based on other immunological parameters. And Dr. Streed noted that this is an area to proceed cautiously with. But we know that various things in the environment -- mercury, viruses, oxidative stress, the methionine deficit, et cetera -- can influence glial function, and once they become activated, their regulation of normal activity may be altered.

So a translational medicine by directional approach is what we're asking for, which is clinician to researcher. We have a lot of data. People like me have a lot of data that we can

share with you to maybe fine-tune your approach to biomarkers. And at the same time, we want to get the information from you guys, and I've been very impressed with where NIH is going. I think that the biomarker exposure pattern is going to be really exciting for us long term if we can apply that.

Liz Mumper was one of the doctors who presented. She's the Medical Director of Defeat Autism Now, a group that's been interested in the biomedical approaches to autism, and this shows the various things -- this is the top 23 things that parents of (inaudible comment) worked with clinicians, and this is a modified CGI. Number one on the list is chelation, which is the ability to remove heavy metals or provide antioxidant support, because chelators are also antioxidants, so their effect may be as a redox benefit. Seventy-six percent got better; two percent got worse in the number-one intervention for that group.

So biomarkers -- we're looking at erythrocytes to see what's there, we're looking at porphyrins,

we're looking at oxidized RNA. Eight-hydroxyguanosine is a very intriguing marker for oxidative stress that you can look at in the urine. It's been published, and we like and see correlation with that. Sometimes you have to get blood, look at cysteine, methionine and other biomarkers like reduced and oxidized lidothione. And then, immunologically, neopterin and biopterin have been published. We're reproducing some of that data, and it looks very exciting, but a variety of autoantibodies are available that have been described to the brain.

So what is our strategic plan? An environment gene and metabolic interaction genes exacerbate the central nervous system damage. How do we find those? And I think this is an area where NIEHS can overlap a lot with what we're trying to accomplish. How might the maturation process, the developmental process influence gene expression, because all genes are not going to be expressed equally at different times in the development phase. So what are the critical mechanisms on how those interactions between toxins and the gene

actually work? How do they their mischief? And is there evidence to suggest that some of these same mechanisms that Dr. Schwartz may be looking at with his group are also going to be related to autism and other neurodevelopmental disorders?

So how do we translate this? Clinicians are developing helpful interventional models around a combined neuroimmunotoxicological theory of autism. And I would say that, within the group of clinicians that I work with, that's kind of our underlying premise in how we treat kids. We intervene on those areas, and we see results that are very favorable in many cases. There's a need to improve those biomarkers, to expand those biomarkers, to validate those biomarkers both for intervention and safety and then enhance the bidirectional effort between clinician and researchers.

So what are the most fruitful places that we think you can get started would be to rigorously investigate the predictive value of the biomarkers and endophenotypic characteristics in both autism and other neurodevelopmental diseases for

identification of causal pathways, the things that are really going wrong, and then how do we develop safe and effective treatment options for the parents that can be validated with good science and then controlled investigations into the treatment approaches with documentation of pretreatment, of post-treatment changes and behavior, biochemical, physiological, immunological, and then both things that may be extra brain, like gut and immune factors and then specific investigations into candidate environmental exposures.

We have focused a lot on mercury, but that's because it's easy to measure and it's relatively inexpensive to measure. Some of the other intoxicants are very complex. There are not good standards for them, and they're extremely expensive. A good environmental toxicant panel costs about $8,000, and I'm not sure what I would do with the data if I found it, I found a lot of things that were positive.

So the overall implementation -- these research goals and activities would have the

greatest likelihood of implementation if NIH would make them priorities in practice and the means to accomplish them are, we hope anyway, to include these activities as an item to be scored when reviewing grant proposals, to list them as program project grants and to encourage the Autism Centers of Excellence to evaluate tests and research environmental factors, biomarkers, and to explore clinical interventions into autism that deal with these biological disorders.

And with that, I thank you very much for your patience at this late hour in the day.

Dr. Insel: Thank you, Jeff. We have 5 minutes.

(Applause)

Dr. Insel: Questions or discussion?

Dr. Bradstreet: Did I make it on time? Amazingly, I did.

Dr. Insel: Terrifically well.

Dr. Bradstreet: Thank you.

Dr. Insel: No comments? No questions?

Dr. Bradstreet: Thank you very much.

Dr. Insel: I think you've explained everything. Thank you. We've reached that part of

the meeting where we open this session up for public comment. Question here? Is this a public comment or a question for Jeff? Public comment. No, I think -- go ahead. Just I was going to say for public comments, just please identify who you are for the tape, and we're going to keep thee relatively short because it's getting late. Thank you.

Mr. Mark Corrales: Sure. Thanks. My name is Mark Corrales. I'm with the U.S. Environmental Protection Agency, although my comments are public comments rather than official comments from the EPA. I had a quick comment on the presentation, and then I wanted to say something about the matrix. The comment on the presentation -- some people argue that environmental factors can't necessarily play a very large role in autism spectrum disorders because the heritability estimates are so high. I just want to mention, as some people pointed out, it is possible that there are not rare but fairly ubiquitous common environmental factors, toxins let's say, that would hide in the heritability estimate, and I

think that's something important to keep in mind. So I can provide some written comments explaining that further if anyone wants.

On the matrix, I think that the group has done a great job. I wish I could have been a part of the workshops. I didn't hear about them, but a couple of thoughts on the matrix. The audience for the matrix, as I understand it, is multifaceted. It's this group. It's Congress, funders and so on, public researchers, practitioners. And I think the purpose is, in part at least, to help prioritize and identify gaps. And I think it would be very useful for identifying gaps if the categories were truly comprehensive and ideally sort of mutually exclusive and parallel in structure.

And the way that it's organized currently, and I don't know if this is something that could be considered for the next iteration of the matrix, the way it's currently organized tends to sort of perpetuate the idea of silos, and it's divided by discipline or methodological approach -- epidemiology, genetics, school-based treatments, interventions.

I think it would be interesting and useful if you could think about structuring the matrix using some different categories, and I think someone referred to those as sort of crosscutting. But I think in some ways, those are the more important categories, and those might be things like specific substantive areas or pathways or avenues of investigation. And it could be multidimensional, so one way to categorize them would be brain regions or systems or pathways; another might be along the core traits and sort of symptoms behaviors and skills; another might be to split it up according to various -- so, for example, are we focusing all of our attention on amygdala but not much is being done in the area of the cerebellum, let's say, or serotonin versus oxytocin versus dopaminergic -- those sorts of things. The sulfur metabolism, how much work is being done there? Is there much funding there? Brain development, neuroligands, BDNF, those sorts of things. So immune, inflammation.

So I think there's some other ways that you systematically split up all the possible avenues

of research. And, ideally, those key words or those categories would come from ontologies that are already out there that people have put a lot of work into so that they were truly comprehensive, and you could really see of all the possible options or all the possible avenues of research -- which ones are being funded, which ones are not being addressed -- and then start to use, ideally, some quantitative metrics to compare those and prioritize. And some of those quantitative measures would be something else to talk about maybe further down the line, but ideally you'd want to look at risk factors and measure them in some sort of common quantitative metrics like, well, at least relative risk, or maybe some of these ideas like false-positive report probability, which is in something in the literature, epidemiological.

But the categories that are in there now -- epidemiology, genetics, and so on -- I think of those as methodologies that can address any one of the stages of development of autism and any one of the pathways. Genetics work can focus on any one

of several important pathways. So I'll stop there in the interest of time --

Dr. Insel: Okay. Thank you.

Mr. Corrales: -- but I appreciate the opportunity for public comment.

Dr. Insel: Great. Well, actually, this comment was one that we talked a lot about at the meeting, and it was the frustration of having, I think, eight areas that seemed to be in some ways silos that needed to be broken down. And that's why, going forward, we were talking about trying to bring these groups together under three major headings. Other comments?

Ms. Wendy Fournier: My name is Wendy Fournier. I'm President of the National Autism Association, and I'm here today to ask that autism be officially declared a national emergency. That is what we believe it is. We have 1 in 166 now diagnosed. Our schools are overburdened. Society is woefully unprepared to handle what lies in the future as these children become adults unless we can find some meaningful treatments that are effected now. For the past year and a half, many

of us in this room, together with parents from across the country, have worked really hard on the Combating Autism Act, a $900 million dollar bill for autism. And we've been working on that to ensure the necessary funding is made available to the most promising areas of research for our children, the role of environmental assailants in the development of autism.

Without a program of intense investigation on environmental factors, effective treatments for our kids will continue to elude us. We need the efforts of this Committee to help steer research initiatives in the right direction, and we need the advocacy groups still involved in negotiating the CAA to stand together during these final negotiations and demand a directive from Congress to fund this desperately needed research. We are at “fourth and inches” right now -- we are so close to getting the environmental research, and our goal, Dr. Schwartz, is to come to you in a few weeks and say, hey, here's $45 million dollars, will you do our research for us. That's our goal.

Study after study has been conducted in the

pursuit of an elusive genetic cause for autism to this date in areas that can be best described as interesting but have no practical application for the children that are suffering right now. I'm referring to facial recognition studies, television viewing habits, Silicon Valley Geek theories. All these things are interesting to some, but they're not helping the children that are affected that need help desperately right now.

The best hope that our children have lies here with you. The suffering that they endure daily -- impaired motor skills and ability to speak, gastrointestinal pain, constipation, and a slew of other physical abnormalities -- will not be healed by the vague sociological or genetic research that continue to get the lion's share of available funds. We need to move into a more practical and productive area of research, research that will address what's going on biomedically with our children and lead us to effective clinical treatments. And to quote my very brilliant friend, Jim Moody, we need to change the paradigm of autism, change the thinking from an inheritable,

untreatable disease to a triggered and therefore preventable and treatable disorder.

I think you should also consider adding experts to your panels in the fields of toxicology, immunology, and gastroenterology since that's where the science is leading us for our children. As you continue to update the matrix, I hope that you will consult those types of experts. It really is the most promising area of research that's open to us, and it may well hold the key for the many hundreds of thousands of children who have been waiting for years for our help. And as a Nation, we just simply can't afford to wait any longer. So thank you very much for your efforts, and I hope you will point in the direction of the environmental research. Thank you.

Dr. Insel: Thank you. Other comments or public points?

[No response]

Dr. Insel: Okay. Well, we've had a very full day starting with the recommendations to the American Academy of Pediatrics and then going through a number of other areas. Do we have

another comment? Good. Thank you.

Ms. Schissel: Hi. I'm Pat Schissel. I'm not prepared, and I certainly don't want to take money away that may be going, you know, for government research, and I do believe that there -- you know, I'm not a researcher -- I'm a social worker, I'm a parent -- let me take a minute -- I believe there's probably an environmental insult, but I believe money needs to go into education, to medical people who, to this day, do not know enough, to educators, to this day who do not know enough, to the man on the street who doesn't know enough -- with all of the public service stuff that's going on, that's great, and whatever we can do in that way. I think ASA has expanded enormously. I think we're seeing across the lifespan much more. You know, you heard it more today in terms of seeing somebody do a presentation and show their child who's an adult or near an adult. But I think to weigh heavily, as the last comment, that it's the environment, I answer probably over 2,000 calls a year on a hotline, and then I get to meet the parents and

the families. It's genetic, and I'm one of them. I mean I have a child, so I say it, you know, with all humility. Unless it's an adoption, it's in the families, and certainly there may indeed be an environmental impact, and I don't say not to do that research, but there are just too many physicians who don't have the wherewithal. It's not taught enough in the medical schools. It's not taught enough in the schools of education. I teach on the graduate level. They come to me in specialized programs. They know nothing about higher functioning autism. You know, if they don't see it and it's not obvious, then they don't know it. So I leave you with that. You know, just we need the money, certainly, and I think that, you know, all that we're presenting, it's got to have an impact. The matrix has to have an impact at Congress, at the congressional level in government. So thank you.

Dr. Insel: Thank you. I would just recall the slide that David Amaral showed, which made, I think, the key point, which is that it's both, genetic and environmental.

Ms. Schissel: Absolutely. I just didn't want the day to end on, you know, it's the environment. That's all.

Dr. Insel: Well, you know, we -- it is in fact the environment, and it is in fact genetic, and it is in fact probably many other things that we don't understand. All the more reason why we have to redouble our efforts to learn more about what causes this and best to treat it. And on that note, I think we are finished until -- we have one more comment from Laura.

Ms. Laura Bono: Yes, thanks. I'm just wondering, because I agree that there is a genetic susceptibility to autism, which, of course, an environmental factor is triggering, otherwise you can't have a genetic epidemic. But that said, I agree that there does need to be money into services. There needs to be money in all of these areas. So my question is to all of you -- how can we as a group, and maybe it's a press release, maybe it's a press conference, how do we with, with Dr. Raub in the room here, how do we as a bunch of autism organizations, NIH groups, declare

autism as an epidemic, declare it a national emergency, just like the AIDS community did, and get the money pouring in that we need? Because it's everywhere. We need money for schools. We need money for services. We need money for homes. We need money for early intervention. We need money for all sorts of research. So that's my question, and I would love for everyone to brainstorm of how we can do that and make sure that in doing so, the money gets funded where it needs to go. Thanks. I'm Laura Bono, National Autism Association.

Dr. Insel: Well, Laura, there are many things that we can try to answer, but one thing that the Federal partners can't do is to tell you how to lobby or how to ask for money. We are legally banned from doing that. And I must say, you've done a very good job without us, so I'm not sure that our advice would be helpful to you anyway.

So the question, though, about how to increase visibility, I think most of you know that the next issue of “Newsweek,” which will be out on Monday or Tuesday, will have, I believe, a cover article

on autism. There's a huge amount of publicity. I think if the Combating Autism Act does, in fact, pass in this session, there will be another bump in publicity. So awareness is much greater than it's ever been. Obviously, that's not enough, and we have to do much, much more.

I do think we're finished. We'll meet again on the 15th of May, 2007. Thank you.

(Whereupon, the IACC meeting was adjourned at 3:52 p.m.)